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- (71) Applicant: **KING PHARMACEUTICALS RESEARCH AND DEVELOPMENT, INC.** [US/US]; 7001 Weston Parkway, Suite 300, Cary, NC 27513 (US).

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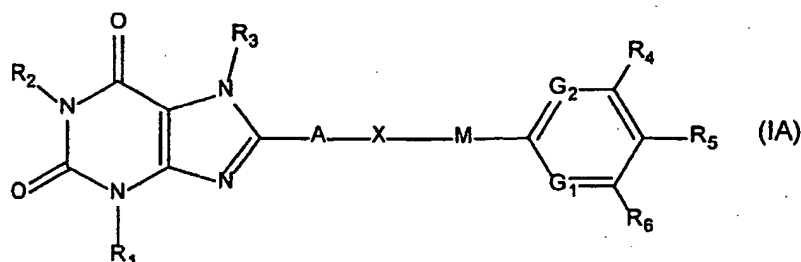
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **BARALDI, Pier, Giovanni** [—/IT]; Via Tulipani, 73, I-44100 Ferrara (IT). **BOREA, Pier, A.** [—/IT]; Via del Turco, 14, I-44100 Ferrara (IT).
- (74) Agents: **KONIECZNY, J., Mark et al.**; Edwards & Angell, LLP, P.O. Box 9169, Boston, MA 02209 (US).

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(54) Title: **8-HETEROARYL XANTHINE ADENOSINE A<sub>2B</sub> RECEPTOR ANTAGONISTS**



(57) Abstract: The present invention relates to compounds of formula (IA): the preparation thereof, pharmaceutical formulations thereof, and their use in medicine as potent or selective A<sub>2B</sub> adenosine receptor antagonists and their uses for treating asthma, autoimmune diseases and retinal vascular diseases.

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# SPECIFICATION

## 8-Heteroaryl Xanthine Adenosine A<sub>2B</sub> Receptor Antagonists

### Related Application

- [01]** This application claims the benefit of U.S. Provisional Application 60/353,317 filed February 1, 2002.

### Background of the Invention

- [02]** The present invention relates to compounds having antagonistic activity on adenosine A<sub>2B</sub> receptors. Such compounds are useful in medicaments for treating diseases responsive to reduced levels of A<sub>2B</sub> receptors as well as use as radioligands for studying biological activity associated with the adenosine A<sub>2B</sub> receptor.
- [03]** Adenosine (Ado) is an autocoid (or local hormone) that modulates numerous functions in the cardiovascular and other organ systems. The actions of Ado are mediated by at least four subtypes of cell surface receptors called A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>. Because the ubiquity of adenosine receptors (AdoRs) throughout the body of a human, their indiscriminate activation may cause undesirable side effects. Therefore, new drug design approaches to achieve receptor and organ selectivity are needed.
- [04]** Recently significant advancement has been made in the understanding of the molecular pharmacology and physiology of A<sub>2B</sub> adenosine receptors. However, due to the lack of highly potent and selective ligands for this receptor subtype, many questions about the patho-physiological role of A<sub>2B</sub> receptors have not yet been answered (Feoktistov and Biaggioni, 1997; Feoktistov and Biaggioni, 1998). A<sub>2B</sub> receptors have been implicated in the regulation of mast cell secretion (Feoktistov and

Biaggioni 1995), gene expression (Boyle *et al.* 1996), cell growth (Dubey *et al.*, 1996), intestinal functions (Murthy *et al.*, 1995), neurosecretion (Mateo *et al.*, 1995), vascular tone (Haynes *et al.*, 1995) and asthma (Feoktistov *et al.*, 1998).

- [05] U.S. Patent 6,117,878 to Linden discloses the use of 8-phenyl substituted xanthines for the treatment of diseases induced by activation of the adenosine A<sub>2B</sub> receptor and mast cell activation. These disease states are disclosed as including asthma, myocardial reperfusion injury, allergic reactions including rhinitis, poison ivy induced responses, urticaria, scleroderma arthritis, other autoimmune diseases and inflammatory bowel diseases. In general, antagonists of the A<sub>2B</sub> adenosine receptor subtype are disclosed to have anti-inflammatory action. U.S. Patent 6,117,878 to Linden is incorporated by reference.
- [06] U.S. Patent Application 2002/0002142 to Belardinelli *et al.* discloses the use of A<sub>2B</sub> adenosine receptor antagonist compounds for inhibiting mammalian cell proliferation in cells that express the A<sub>2B</sub> adenosine receptor including human retinal endothelial cells (HREC). Belardinelli discloses such treatment for ischemic injury to retinal vessels, for example, microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy. U.S. Patent Application 2002/0002142 to Belardinelli *et al.* is incorporated by reference.
- [07] The use of A<sub>2B</sub> antagonists as antiasthmatic agents is supported by the experimental observation that theophylline and enprofylline are used as therapeutic agents (Feoktistov and Biaggioni 1997; Feoktistov *et al.*, 1998). Theophylline is an alkyl-xanthine that is a weak nonselective adenosine antagonist (See Linden *et al.*, *Cardiovascular Biology of Purines*, eds. G. Burnstock, *et al.*, 1998, pp 1 – 20.) However, its use is associated with unpleasant side effects, such as insomnia and diuresis. (See Vassallo *et al.*, *Mayo. Clin. Proc.* 1998, 73, 346-354) In recent years, the use of theophylline as a bronchodilator, for relief of asthma, has been supplanted by drugs of other classes, *i.e.*, selective  $\beta_2$ -adrenergic

agonists, corticosteroids, and recently leukotriene antagonists. (See Drazen *et al.*, *New Eng. J. Med.* 1999, 340, 197-206.) These compounds also have limitations, thus, the development of a theophylline-like drug with reduced side effects is still desirable.

**[08]** It has been recognized that theophylline and its closely related analogue caffeine block endogenous adenosine acting as a local modulator of adenosine receptors in the brain and other organs at therapeutically useful doses. (See Fredholm *et al.*, *Pharmacol. Rev.* 1999, 51, 83-133.) In comparison to the other known actions of theophylline, *e.g.*, inhibition of phosphodiesterases, theophylline is more potent in antagonism of adenosine receptors.

**[09]** As noted the xanthine derivative, enprofylline, is also used to treat asthma. Enprofylline has been reported to block  $A_{2B}$  adenosine receptors. However, this compounds only weakly blocks  $A_1$ ,  $A_{2A}$  and  $A_3$  adenosine receptors.

**[10]** It has been reported that therapeutic concentrations of theophylline or enprofylline block human  $A_{2B}$  receptors, and it has been proposed that antagonists selective for this subtype may have potential use as antiasthmatic agents. (See Feoktistov *et al.*, *Pharmacol. Rev.* 1997, 49, 381-402; and Robeva *et al.*, *Drug Dev. Res.* 1996, 39, 243-252. Enprofylline has a reported  $K_i$  value of 7  $\mu$ M and is somewhat selective in binding to human  $A_{2B}$  adenosine receptors. (See Robeva *et al.*, *Drug Dev. Res.* 1996, 39, 243-252 and Linden *et al.*, *Vol. Pharmacol.* 1999, 56, 705-713.)

**[11]** Adenosine  $A_{2B}$  receptors are expressed in some mast cells, such as the BR line of canine mastocytoma cells, which appear to be responsible for triggering acute  $Ca^{2+}$  mobilization and degranulation. (See Auchampach *et al.*, *Mol. Pharmacol.* 1997, 52, 846-S60 and Forsyth *et al.*, *Inflamm. Res.* 1999, 48, 301-307.) Adenosine  $A_{2B}$  receptors also trigger  $Ca^{2+}$  mobilization, and participate in a delayed IL8 release from

human HMC-1 mast cells. Other functions associated with the A<sub>2B</sub> AR are the control of cell growth and gene expression, (See Neary *et al.*, *Trends Neurosci.* 1996, 19, 13-18.) endothelial-dependent vasodilation (See Martin *et al.*, *J Pharmacol. Exp. Ther.* 1993, 265, 248-253.), and fluid secretion from intestinal epithelia. (See Strohmeier, *et al.*, *J Biol. Chem.* 1995, 270, 2387-2394.) Adenosine acting through A<sub>2B</sub> receptor subtype has also been reported to stimulate chloride permeability in cells expressing the cystic fibrosis transport regulator. (See Clancy *et al.*, *Am. J Physiol.* 1999, 276, C361-C369.)

- [12] Both of these xanthine derivatives, enprofylline and theophylline, are proven to be effective but with low potency and selectivity at the A<sub>2B</sub> adenosine receptor subtype (theophylline A<sub>2B</sub> binding affinity K<sub>i</sub> = 13 µM; enprofylline A<sub>2B</sub> binding affinity K<sub>i</sub> = 7 µM).
- [13] Asthma is a complex disease involving the concerted actions of multiple inflammatory and immune cells, spasmogens, inflammatory mediators, cytokines and growth factors. Theophylline has significant side effects that may be related to its A<sub>1</sub> receptor antagonism. It is therefore believed that more potent and selective A<sub>2B</sub> receptor antagonists will provide enhanced asthma treatment.
- [14] The A<sub>1</sub>, A<sub>2A</sub> and A<sub>3</sub> adenosine receptors have been pharmacologically characterized through the use of highly potent and selective agonists and/or antagonists. In contrast the study of A<sub>2B</sub> receptor has been precluded due to the lack of selective ligands. Researchers such as Jacobson and his coworkers have proposed using the radioligand of 7-amino-2-(2-4-furyl)-5-[2-(4-hydroxy-phenyl)ethyl]-amino[1,2,4]-triazolo-[1,5-a][1,3,5]-triazine ([<sup>3</sup>H]-ZM241385) as useful radioligand for studying the A<sub>2B</sub> adenosine receptor subtype (Ji *et al.*, 1999) even though [<sup>3</sup>H]-ZM241385 has a K<sub>D</sub> value of 34 nM.
- [15] Jacobson and coworkers have also reported some xanthine derivatives endowed with good affinity to the adenosine receptors but without

significant selectivity for the human A<sub>2B</sub> adenosine receptor subtype (Kim *et al.*, 1999; Jacobson *et al.*, 1999). Some non-xanthine derivatives closely related to ZM 241385 have also been synthesized, but, while some of the reported compounds displayed significant affinity to A<sub>2B</sub> receptors, none of them possessed relevant selectivity versus the other receptor subtypes A<sub>1</sub>, A<sub>2A</sub> and A<sub>3</sub> (De Zwart *et al.*, 1999).

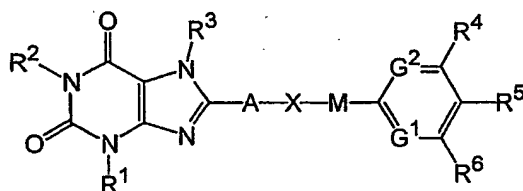
- [16] Similarly, Jacobson and coworkers, with the aim of obtaining non-xanthine antagonists for A<sub>2B</sub> receptors, modified the structure of 5-amino-9-chloro-2-(2-furanyl)[1,2,4]triazolo-[1,5-c]-quinazoline (CGS 15943), a non selective adenosine receptor antagonist, which appeared to be a suitable starting compound for adenosine receptor antagonists by appropriate substitutions at different positions. In particular an improvement of affinity to A<sub>2B</sub> receptors was observed when aminoacidic chains are appended to the amino group of position 5 (Kim *et al.*, 1998).
- [17] U.S. Patent 5,935,964 to Baraldi *et al.* discloses triazolo pyrimidines have antagonist affinity for the A<sub>2A</sub> receptor. Using these compounds as a starting point, Baraldi *et al.* investigated a series of pyrazolo[4,3-e]1,2,4-triazolo-[1,5-c]pyrimidine compounds for use as A<sub>2B</sub> receptor antagonists. In particular the compounds with the free amino group at the 5-position, and for example, a phenylethyl chain at the N8 pyrazole nitrogen show good affinity to A<sub>2B</sub> adenosine receptors. However, none of these compounds demonstrated good selectivity (Baraldi *et al.*, 2001).
- [18] Linden, Jacobson and coworkers have also reported a series of anilide derivatives of 8-phenyl-xanthine carboxylic congeners that proved to be potent and selective A<sub>2B</sub> antagonists (Kim *et al.*, 2000; Ji *et al.*, 2001) and S-substituted 1,3,7-trialkyl xanthine derivatives (U.S. Patent 5,861,405 to Jacobson *et al.*) While many of the Linden and Jacobson compounds have high adenosine A<sub>2B</sub> potency, selectivity against other human adenosine receptors are in most cases limited (PCT patent application WO 00/73307 by Linden, Jacobson *et al.*, 2000).

- [19] We have now discovered additional novel xanthine compounds having high antagonist affinity for the  $A_{2B}$  receptor with varying levels of affinity and superior selectivity compared to compounds previously reported. The above noted references are incorporated herein by reference.

## Brief Summary of the Invention

- [20] Compounds useful as potent, yet selective modulators of adenosine receptors, with activity as adenosine  $A_{2B}$  receptor antagonists, and, in some cases  $A_1$  or  $A_3$  antagonists, and methods of preparation and use thereof, are disclosed.
- [21] The compounds of the present invention have the following general formulas.

- [22] Formula I:



wherein:

$R^1$  and  $R^2$  are independently hydrogen,  $(C_1$  to  $C_8)$ alkyl,  $(C_2$  to  $C_8)$ alkenyl,  $(C_2$  to  $C_8)$ alkynyl,  $(C_7$  to  $C_{14})$ aralkyl,  $(C_8$  to  $C_{14})$ aralkenyl, or  $(C_8$  to  $C_{14})$ aralkynyl;

$R^3$  is hydrogen,  $(C_1$  to  $C_4)$ alkyl,  $(C_2$  to  $C_5)$  alkenyl, or  $(C_2$  to  $C_5)$  alkynyl);

A is a carbon-carbon bond, alkyl chain of one to four carbons, alkenyl chain of two to four carbons, or alkynyl chain of two to four carbons;

X is a five or six-membered heteroaromatic ring, containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen;

M is a (C<sub>1</sub> to C<sub>8</sub>)alkylene, (C<sub>2</sub> to C<sub>8</sub>)alkenylene, or (C<sub>2</sub> to C<sub>8</sub>)alkynylene, wherein at least one of the carbon atoms of the alkylene, alkenylene, or alkynylene group is present as a carbonyl, and one or more of the remaining carbon atoms of the alkylene, alkenylene, or alkynylene group may be replaced by -O-, -N(R<sup>7</sup>)-, -S-, -S(O)-, or -SO<sub>2</sub>-;

G<sup>1</sup> and G<sup>2</sup> are independently CH or N;

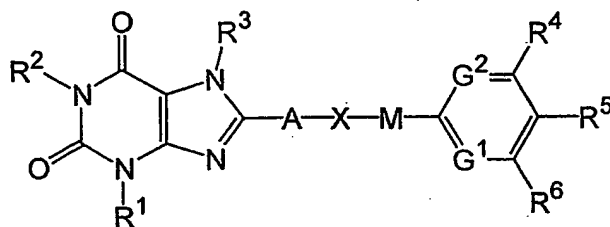
R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>)alkenyl, (C<sub>2</sub> to C<sub>5</sub>)alkynyl, (C<sub>6</sub> to C<sub>10</sub>)aryl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl, acyl, alkoxy, aralkoxyalkylthio, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, iodo, nitro, cyano, azido, hydroxy, sulfhydryl, S(O)alkyl, S(O)<sub>2</sub>alkyl, CO<sub>2</sub>H, SO<sub>3</sub>H, or five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from nitrogen, oxygen, or sulfur; or

taken together either R<sup>4</sup> and R<sup>5</sup> or R<sup>5</sup> and R<sup>6</sup> may independently form a carbocyclic or heterocyclic fused ring selected from the group of fused rings comprising -OCH<sub>2</sub>O-, -OCH(R<sup>7</sup>)O-, -OC(R<sup>7</sup>)<sub>2</sub>O-, -OCH<sub>2</sub>CH<sub>2</sub>O-, OCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>O-, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O-, -OCH=CH-, -CH=CH-O-, -O-CH=CH-O-, -CH=CH-CH=CH-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; and

R<sup>7</sup> is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl).

[23] In another aspect this invention provides compounds of the following Formula II:





wherein:

R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl;

R<sup>3</sup> is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl);

A is a carbon-carbon bond, alkyl chain of one to four carbons, alkenyl chain of two to four carbons, or alkynyl chain of two to four carbons;

X is independently a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen; a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen, substituted at any position with a substituent selected from lower alkyl, amino, hydroxy, alkyloxy, acyloxy, and acylamino; or a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen, substituted at any two positions with substituents selected independently from lower alkyl, amino, hydroxy, alkyloxy, acyloxy, and acylamino.

M is a (C<sub>1</sub> to C<sub>8</sub>)alkylene, (C<sub>2</sub> to C<sub>8</sub>)alkenylene, or (C<sub>2</sub> to C<sub>8</sub>)alkynylene, wherein at least one of the carbon atoms of the alkylene, alkenylene, or alkynylene group is present as a carbonyl, and one or more of the

remaining carbon atoms of the alkylene, alkenylene, or alkynylene group may be replaced by  $-O-$ ,  $-N(R^7)-$ ,  $-S-$ ,  $-S(O)-$ ,  $-SO_2-$ ; or a carbon substituted with a lower alkyl.

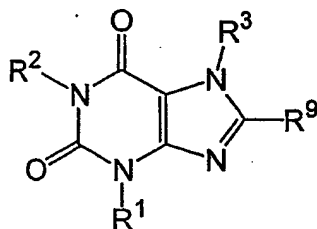
$G^1$  and  $G^2$  are independently CH or N;

$R^4$ ,  $R^5$  and  $R^6$  are independently hydrogen,  $(C_1 \text{ to } C_4)\text{alkyl}$ ,  $(C_2 \text{ to } C_5)\text{alkenyl}$ ,  $(C_2 \text{ to } C_5)\text{alkynyl}$ ,  $(C_6 \text{ to } C_{10})\text{aryl}$ ,  $(C_7 \text{ to } C_{14})\text{aralkyl}$ ,  $(C_8 \text{ to } C_{14})\text{aralkenyl}$ , or  $(C_8 \text{ to } C_{14})\text{aralkynyl}$ , acyl, alkoxy, aralkoxyalkylthio, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, iodo, nitro, cyano, azido, hydroxy, sulfhydryl,  $S(O)\text{alkyl}$ ,  $S(O)_2\text{alkyl}$ ,  $CO_2H$ ,  $SO_3H$ , or five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from nitrogen, oxygen, or sulfur; or

taken together either  $R^4$  and  $R^5$  or  $R^5$  and  $R^6$  independently may form a carbocyclic or heterocyclic fused ring selected from the group of fused rings comprising  $-OCH_2O-$ ,  $-OCH(R^7)O-$ ,  $-OC(R^7)_2O-$ ,  $-OCH_2CH_2O-$ ,  $-OCH_2CH_2-$ ,  $-CH_2CH_2O-$ ,  $-OCH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2O-$ ,  $-OCH=CH-$ ,  $-CH=CH-O-$ ,  $-O-CH=CH-O-$ ,  $-CH=CH-CH=CH-$ ,  $-CH_2CH_2CH_2-$  and  $-CH_2CH_2CH_2CH_2-$ ; and

$R^7$  is hydrogen,  $(C_1 \text{ to } C_4)\text{alkyl}$ ,  $(C_2 \text{ to } C_5)\text{alkenyl}$ , or  $(C_2 \text{ to } C_5)\text{alkynyl}$ .

[24] In a further aspect, this invention provides compounds of the following Formula III

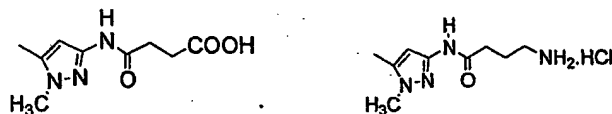


wherein:

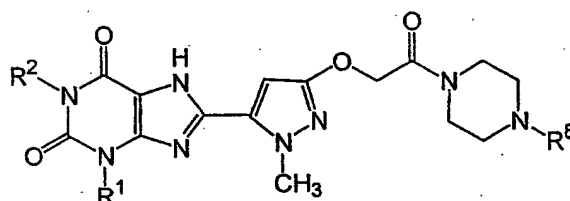
$R^1$  and  $R^2$  are independently hydrogen,  $(C_1 \text{ to } C_8)\text{alkyl}$ ,  $(C_2 \text{ to } C_8)\text{alkenyl}$ ,  $(C_2 \text{ to } C_8)\text{alkynyl}$ ,  $(C_7 \text{ to } C_{14})\text{aralkyl}$ ,  $(C_8 \text{ to } C_{14})\text{aralkenyl}$ , or  $(C_8 \text{ to } C_{14})\text{aralkynyl}$ ;

$R^3$  is H or  $(C_1 \text{ to } C_8)\text{alkyl}$ ; and

$R^9$  is independently a phenyl or pyrazole ring; a phenyl or pyrazole ring substituted at any position with amino, lower alkyl, or carboxyl; or a phenyl or pyrazole ring substituted at any two positions with a substituent selected from amino, lower alkyl, and carboxyl; or



[25] In yet another aspect, the invention provides compounds of Formula IV:



wherein:

$R^1$  and  $R^2$  are independently hydrogen,  $(C_1 \text{ to } C_8)\text{alkyl}$ ,  $(C_2 \text{ to } C_8)\text{alkenyl}$ ,  $(C_2 \text{ to } C_8)\text{alkynyl}$ ,  $(C_7 \text{ to } C_{14})\text{aralkyl}$ ,  $(C_8 \text{ to } C_{14})\text{aralkenyl}$ , or  $(C_8 \text{ to } C_{14})\text{aralkynyl}$ ; and

$R^8$  is phenyl, substituted phenyl,  $(C_1 \text{ to } C_8)\text{alkyl}$ , or benzyl.

[26] The compounds can be used in a method for the treatment of diseases mediated by adenosine  $A_{2B}$  receptors. Such diseases include, but are not limited to chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis

and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; and apnea of preterm infants; myocardial reperfusion injury, inflammatory bowel disease, and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis (MS), and lupus erythematosus.

[27] Similarly, the compounds can be used in a method for the treatment of diseases involving microvascular abnormalities of the retina that are mediated by adenosine  $A_{2B}$  receptors. Such diseases include, but are not limited to, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

[28] The compounds can be used in a pharmaceutical formulation that includes a compound of the present invention and one or more excipients. Various chemical intermediates can be used to prepare the compounds of the present invention.

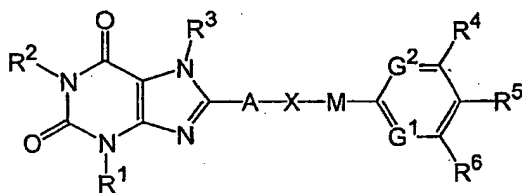
### Brief Description of the Drawings

- [29] *Figure 1* illustrates competition binding curves for compound AS29 to human cloned  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$ , and  $A_3$  adenosine receptors;
- [30] *Figure 2* illustrates competition binding curves for compound AS57 to human cloned  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$ , and  $A_3$  adenosine receptors;
- [31] *Figure 3* illustrates competition binding curves for compound AS64 to human cloned  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$ , and  $A_3$  adenosine receptors;
- [32] *Figure 4* illustrates competition binding curves for compound AS68 to human cloned  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$ , and  $A_3$  adenosine receptors; and
- [33] *Figure 5* illustrates a Comparison between binding and functional data.

## Detailed Description of the Invention

- [34] The present application discloses compounds useful as potent, yet selective antagonists of adenosine receptors with particular utility with the adenosine A<sub>2B</sub> receptor subtype, methods of preparation and use thereof.
- [35] The compounds can be used in a pharmaceutical formulation that includes a compound of the present invention and one or more excipients. Various chemical intermediates can be used to prepare the compounds of the present invention.
- [36] The compounds of the present invention have the following general formulas.

[37] Formula I:



wherein:

R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl;

R<sup>3</sup> is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl);

A is a carbon-carbon bond, alkyl chain of one to four carbons, alkenyl chain of two to four carbons, or alkynyl chain of two to four carbons;

X is a five or six-membered heteroaromatic ring, containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen;

M is a (C<sub>1</sub> to C<sub>8</sub>)alkylene, (C<sub>2</sub> to C<sub>8</sub>)alkenylene, or (C<sub>2</sub> to C<sub>8</sub>)alkynylene, wherein at least one of the carbon atoms of the alkylene, alkenylene, or alkynylene group is present as a carbonyl, and one or more of the remaining carbon atoms of the alkylene, alkenylene, or alkynylene group may be replaced by -O-, -N(R<sup>7</sup>)-, -S-, -S(O)-, or -SO<sub>2</sub>-;

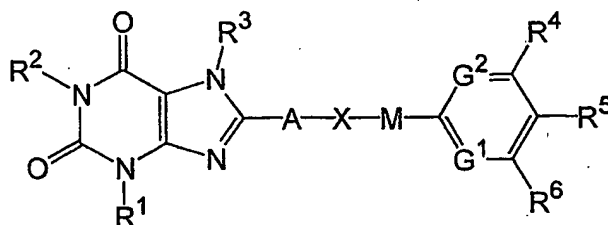
G<sup>1</sup> and G<sup>2</sup> are independently CH or N;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>)alkenyl, (C<sub>2</sub> to C<sub>5</sub>)alkynyl, (C<sub>6</sub> to C<sub>10</sub>)aryl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl, acyl, alkoxy, aralkoxyalkylthio, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, iodo, nitro, cyano, azido, hydroxy, sulfhydryl, S(O)alkyl, S(O)<sub>2</sub>alkyl, CO<sub>2</sub>H, SO<sub>3</sub>H, or five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from nitrogen, oxygen, or sulfur; or

taken together either R<sup>4</sup> and R<sup>5</sup> or R<sup>5</sup> and R<sup>6</sup> may independently form a carbocyclic or heterocyclic fused ring selected from the group of fused rings comprising -OCH<sub>2</sub>O-, -OCH(R<sup>7</sup>)O-, -OC(R<sup>7</sup>)<sub>2</sub>O-, -OCH<sub>2</sub>CH<sub>2</sub>O-, OCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>O-, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O-, -OCH=CH-, -CH=CH-O-, -O-CH=CH-O-, -CH=CH-CH=CH-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; and

R<sup>7</sup> is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl).

[38] In another aspect this invention provides compounds of the following Formula II:



wherein:

R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl;

R<sup>3</sup> is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl);

A is a carbon-carbon bond, alkyl chain of one to four carbons, alkenyl chain of two to four carbons, or alkynyl chain of two to four carbons;

X is independently a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen; a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen, substituted at any position with a substituent selected from lower alkyl, amino, hydroxy, alkyloxy, acyloxy, and acylamino; or a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen, substituted at any two positions with substituents selected independently from lower alkyl, amino, hydroxy, alkyloxy, acyloxy, and acylamino.

M is a (C<sub>1</sub> to C<sub>8</sub>)alkylene, (C<sub>2</sub> to C<sub>8</sub>)alkenylene, or (C<sub>2</sub> to C<sub>8</sub>)alkynylene, wherein at least one of the carbon atoms of the alkylene, alkenylene, or alkynylene group is present as a carbonyl, and one or more of the

remaining carbon atoms of the alkylene, alkenylene, or alkynylene group may be replaced by  $-O-$ ,  $-N(R^7)-$ ,  $-S-$ ,  $-S(O)-$ ,  $-SO_2-$ ; or a carbon substituted with a lower alkyl.

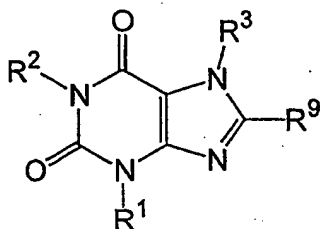
$G^1$  and  $G^2$  are independently CH or N;

$R^4$ ,  $R^5$  and  $R^6$  are independently hydrogen,  $(C_1 \text{ to } C_4)$ alkyl,  $(C_2 \text{ to } C_5)$ alkenyl,  $(C_2 \text{ to } C_5)$ alkynyl,  $(C_6 \text{ to } C_{10})$ aryl,  $(C_7 \text{ to } C_{14})$ aralkyl,  $(C_8 \text{ to } C_{14})$ aralkenyl, or  $(C_8 \text{ to } C_{14})$ aralkynyl, acyl, alkoxy, aralkoxyalkylthio, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, iodo, nitro, cyano, azido, hydroxy, sulfhydryl,  $S(O)$ alkyl,  $S(O)_2$ alkyl,  $CO_2H$ ,  $SO_3H$ , or five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from nitrogen, oxygen, or sulfur; or

taken together either  $R^4$  and  $R^5$  or  $R^5$  and  $R^6$  independently may form a carbocyclic or heterocyclic fused ring selected from the group of fused rings comprising  $-OCH_2O-$ ,  $-OCH(R^7)O-$ ,  $-OC(R^7)_2O-$ ,  $-OCH_2CH_2O-$ ,  $OCH_2CH_2-$ ,  $-CH_2CH_2O-$ ,  $-OCH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2O-$ ,  $-OCH=CH-$ ,  $-CH=CH-O-$ ,  $-O-CH=CH-O-$ ,  $-CH=CH-CH=CH-$ ,  $-CH_2CH_2CH_2-$  and  $-CH_2CH_2CH_2CH_2-$ ; and

$R^7$  is hydrogen,  $(C_1 \text{ to } C_4)$ alkyl,  $(C_2 \text{ to } C_5)$  alkenyl, or  $(C_2 \text{ to } C_5)$  alkynyl).

[39] In a further aspect, this invention provides compounds of the following Formula III



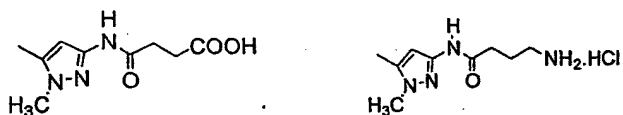


wherein:

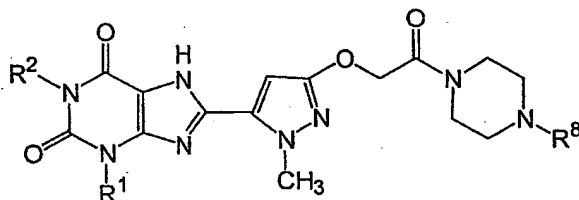
$R^1$  and  $R^2$  are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl;

$R^3$  is H or (C<sub>1</sub> to C<sub>8</sub>)alkyl; and

$R^9$  is independently a phenyl or pyrazole ring; a phenyl or pyrazole ring substituted at any position with amino, lower alkyl, or carboxyl; or a phenyl or pyrazole ring substituted at any two positions with a substituent selected from amino, lower alkyl, and carboxyl; or



[40] In yet another aspect, the invention provides compounds of Formula IV:



wherein:

$R^1$  and  $R^2$  are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl; and

$R^8$  is phenyl, substituted phenyl, (C<sub>1</sub> to C<sub>8</sub>)alkyl, or benzyl.

[41] As used herein the term "very potent adenosine A<sub>2B</sub> receptor antagonist" means a compound able to prevent the inhibition of an adenosine A<sub>2B</sub> receptor agonist and having a binding to human adenosine

A<sub>2B</sub> receptor (K<sub>i</sub>) of less than 2000 nM, preferably less than 150 nM, and most preferably less than 50 nM. The term "highly potent adenosine A<sub>2B</sub> receptor antagonist" means a very potent adenosine A<sub>2B</sub> receptor antagonist having a binding affinity to human adenosine A<sub>2B</sub> receptor (K<sub>i</sub>) of less than 150 nM.

[42] As used herein the term "highly selective adenosine A<sub>2B</sub> receptor antagonist" means a very potent adenosine A<sub>2B</sub> receptor antagonist having having a binding affinity to human adenosine receptor subtypes A<sub>1</sub>, A<sub>2A</sub> and A<sub>3</sub> (K<sub>i</sub>) of greater than 1,000 nM.

[43] As used herein the term "lower alkyl" means a monovalent radical, straight or branched chain, derived from the corresponding alkane having one to ten carbon atoms, *i.e.*, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *t*-butyl, pentyl (all isomers), etc. Likewise, "lower alkylene" means a divalent radical of the corresponding alkane. Further, as used herein, other moieties having names derived from alkanes, such as alkoxyl, alkanoyl, alkenyl, cycloalkenyl, etc when modified by "lower," have carbon chains of ten or less carbon atoms. In those cases where the minimum number of carbons are greater than one, *e.g.*, alkenyl (minimum of two carbons) and cycloalkyl, (minimum of three carbons), it is to be understood that "lower" means at least the minimum number of carbons.

[44] As used herein the term "amino acid" means an alpha amino acid selected from those amino acids that naturally occur in proteins but without regard for specific stereochemical properties. The term "protected amino acid" means an amino acid of which the alpha amino group has been converted to a less reactive moiety, but a moiety that can be converted back to the amino group with relative ease. The terms "amino acid residue" and "amino acid moiety" are use synonymously herein.

[45] As used herein, the term "substituted alkyl" refers to an alkyl group, preferably of from 1 to 10 carbon atoms ("substituted lower alkyl"), having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from

the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-, heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and asymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, aryl, heteroaryl and heterocyclic. As used herein, other moieties having the prefix "substituted" are intended to include one or more of the substituents listed above.

- [46] As used herein, the term "alkoxy" refers to the group "alkyl-O-", where alkyl is as defined above. Preferred alkoxy groups include, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.
- [47] As used herein, the term "alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl (-CH=CH<sub>2</sub>), n-propenyl (-CH<sub>2</sub>CH=CH<sub>2</sub>), iso-propenyl (-C(CH<sub>3</sub>)=CH<sub>2</sub>), and the like.
- [48] As used herein, the term "alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.
- [49] As used herein, the term "acyl" refers to the groups alkyl-C(O)-, substituted alkyl C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)-

where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

[50] As used herein, the term "acylamino" refers to the group  $-C(O)NRR$  where each R is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, or heterocyclic, wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

[51] As used herein, the term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring, (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like. Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents and preferably 1 to 3 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy,  $-SO$ -alkyl,  $-SO$ -substituted alkyl,  $-SO$ -aryl,  $-SO$ -heteroaryl,  $-SO_2$ -alkyl,  $-SO_2$ -substituted alkyl,  $-SO_2$ -aryl,  $-SO_2$ -heteroaryl, trihalomethyl. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

[52] As used herein, the term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 12 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantyl, and the like.

[53] As used herein, the terms "halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is fluoro, bromo or chloro.

- [54] As used herein, the term "heteroaryl" refers to an aromatic carbocyclic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).
- [55] Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with from 1 to 5 substituents and preferably 1 to 3 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl, trihalomethyl. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyll or benzothienyl).
- [56] "Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated carbocyclic group having a single ring or multiple condensed rings, from 1 to 15 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring. Such heterocyclic groups are optionally substituted with 1 to 5 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, aryloxy, halo, nitro, heteroaryl, thiol, thioalkoxy, substituted thioalkoxy, thioaryloxy, trihalomethyl, and the like. Such heterocyclic groups can have a single ring or multiple condensed rings.
- [57] As to any of the above groups that contain 1 or more substituents, it is understood, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

[58] "Pharmaceutically acceptable salts" refers to pharmaceutically acceptable salts of a compound of the general formula of the present invention, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like can be used as the pharmaceutically acceptable salt.

[59] The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, amino or carboxyl groups of the compounds (including intermediates thereof such as the aminolactams, aminolactones, etc.) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, amino or carboxyl group. Preferred removable amino blocking groups include conventional substituents such as t-butyloxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), and the like which can be removed by conventional conditions compatible with the nature of the product.

[60] Those skilled in the art of organic chemistry will appreciate that reactive and fragile functional groups often must be protected prior to a particular reaction, or sequence of reactions, and then restored to their original forms after the last reaction is completed. Usually groups are protected by converting them to a relatively stable derivative. For example, a hydroxyl group may be converted to an ether group and an amino converted to an amide or carbamate. Methods of protecting and de-protect, also know as "blocking" and "de-blocking," are well know and widely practiced in the art, e.g., see T. Green, Protective Groups in Organic Synthesis, John Wiley, New York (1981) or Protective Groups in Organic Chemistry, Ed. J.F.W. McOmie, Plenum Press, London (1973).

[61] Representative example compounds include:

Example Compound Number	Compound Name
AS3	8-(3-amino-1-methyl-1 <i>H</i> -pyrazol-5-yl)-1,3-dipropyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione
AS4	[3-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)isoxazol-5-yl]methylbenzoate
AS7	8-(1-methyl-4-nitro-1 <i>H</i> -pyrrol-2-yl)-1,3-dipropyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione
AS8	4-[[5-(1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]amino]-4-oxobutanoic acid
AS9	<i>tert</i> -butyl 4-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]amino]-4-oxobutylcarbamate
AS10	4-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]amino]-4-oxobutan-1-aminium
AS11	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-phenylacetamide
AS12	2-(2,4-dichlorophenoxy)- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS13	2-(3-methoxyphenyl)- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS14	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(4-isobutylphenyl)acetamide
AS15	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(4-nitrophenyl)acetamide
AS16	2-[4-benzyloxyphenyl]- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS17	2-[4-hydroxyphenyl]- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS18	(2 <i>S</i> )- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-phenylpropanamide
AS19	(2 <i>R</i> )- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-phenylpropanamide
AS20	{3-[( <i>E</i> )-2-(1,3-dipropyl-7-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)vinyl]isoxazol-5-yl}methyl benzoate
AS21	2-(4-chlorophenoxy)- <i>N</i> -[5-(1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS22	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(4-fluorophenyl)acetamide
AS23	2-(4-methoxyphenyl)- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS24	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(3-chlorophenyl)acetamide
AS25	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(3-fluorophenyl)acetamide

AS26	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-[4-( <i>N,N</i> -dimethylamino)phenyl]acetamide
AS27	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(4-chlorophenyl)acetamide
AS28	2-(3,4-dimethoxyphenyl)- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS29	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-[4-[[2-(trifluoromethyl)benzyl]oxy]phenyl]acetamide
AS30	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-[4-[[3-(trifluoromethyl)benzyl]oxy]phenyl]acetamide
AS31	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-[4-(4-nitro-benzyl)oxy]phenyl]acetamide
AS32	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide
AS33	Phenyl 4-[( <i>E</i> )-2-(7-methyl-1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)vinyl]-1-methyl-1 <i>H</i> -pyrrole-2-carboxylate
AS35	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-5-yl]-2-phenylacetamide
AS36	8-(1-methyl-3-nitro-1 <i>H</i> -pyrazol-5-yl)-1,3-dipropyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione
AS37	8-(5-amino-1-methyl-1 <i>H</i> -pyrazol-3-yl)-1,3-dipropyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione
AS38	8-(3-amino-1-methyl-1 <i>H</i> -pyrazol-5-yl)-1,3-dimethyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione
AS40	<i>N</i> -[5-(2,6-dioxo-1,3-dimethyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-phenylacetamide
AS43	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(3,4-difluorophenyl)acetamide
AS44	2-(2,3,4-trimethoxyphenyl)- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS53	<i>N</i> -[4-(dimethylamino)phenyl]- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]urea
AS54	<i>N</i> -(3-chlorophenyl)- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]urea
AS55	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]- <i>N</i> -(3-methoxyphenyl)urea
AS56	2-[4-(benzyl)oxy]-3-methoxyphenyl]- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS57	2-(1,3-benzodioxol-5-yl)- <i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]acetamide
AS58	<i>N</i> -[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-2-(4-hydroxy-3-methoxyphenyl)acetamide
AS59	<i>N</i> -(4-methylphenyl)-2-[[5-(1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]acetamide



AS60	<i>N</i> -(4-bromophenyl)-2-[[3-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-5-yl]oxy]acetamide
AS61	<i>N</i> -(4-fluorophenyl)-2-[[3-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-5-yl]oxy]acetamide
AS62	2-[[3-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-5-yl]oxy]- <i>N</i> -(4-fluorophenyl)acetamide
AS63	2-[[3-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-5-yl]oxy]- <i>N</i> -(4-bromophenyl)acetamide
AS64	2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]- <i>N</i> -(4-fluorophenyl)acetamide
AS65	2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]- <i>N</i> -(4-bromophenyl)acetamide
AS66	2-[[5-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]- <i>N</i> -(4-fluorophenyl)acetamide
AS67	2-[[5-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]- <i>N</i> -(4-bromophenyl)acetamide
AS68	<i>N</i> -1,3-benzodioxol-5-yl-2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]acetamide
AS69	2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]- <i>N</i> -(4-methoxyphenyl)acetamide
AS1	1,3-di- <i>n</i> -propyl-8-(1-methyl-5-carboxy-1- <i>H</i> -pyrazol-3-yl)-xanthine
AS49	1-[5-(2,6-Dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]-3-(4-methoxy-phenyl)-urea
AS91	1,3-di- <i>n</i> -propyl-8-{5-[(4-sec-butyl-phenylcarbamoyl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS92	1,3-di- <i>n</i> -propyl-8-{5-[(4-methyl-phenylcarbamoyl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS93	1,3-di- <i>n</i> -propyl-8-{5-[(4-(morpholine-4-yl)-phenylcarbamoyl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS95	1,3-di- <i>n</i> -propyl-8-{5-[(4-carboxy-phenylcarbamoyl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS99	1,3-di- <i>n</i> -propyl-8-{5-[(3,4-dimethyl-phenylcarbamoyl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS100	1,3-di- <i>n</i> -propyl-8-{5-[(3,4-dimethyl-phenylcarbamoyl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS101	1,3-di- <i>n</i> -propyl-8-{5-[(3,4-dimethoxy-phenylcarbamoyl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS89	1,3-di- <i>n</i> -propyl-8-{5-[(pyridin-4-yl)-methoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS70	1,3-di- <i>n</i> -propyl-8-{5-[2-oxo-2-(4-phenyl-piperazin-1-yl)-ethoxy]-2-methyl-2 <i>H</i> -pyrazole-3-yl}-xanthine
AS72	8-(5-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-2-methyl-2 <i>H</i> -pyrazol-3-yl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione

AS87	1,3-di-n-propyl-8-{5-[2-Oxo-2-(4-methyl-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine
AS90	8-(5-{2-[4-(4-Benzyl-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-2-methyl-2H-pyrazol-3-yl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione
AS96	1,3-di-allyl-8-{5-[2-oxo-2-(4-phenyl-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine
AS74	1,3-di-n-propyl-8-{3-[(3,4-methylenedioxy-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine
AS76	1,3-di-n-propyl-8-{3-[(3,4-dimethoxy-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine
AS73	1,3-di-n-propyl-8-{3-[(4-fluoro-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine
AS75	1,3-di-n-propyl-8-{3-[(4-methoxy-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine
AS81	1,3-di-n-propyl-8-{6-[(4-iodo-phenylcarbamoyl)-methoxy]-pyridin-3-yl}-xanthine
AS85	1,3-di-n-propyl-8-{6-[(4-iodo-phenylcarbamoyl)-methoxy]-pyridazin-3-yl}-xanthine
AS68a	<i>N</i> -1,3-benzodioxol-5-yl-2-[[5-(2,6-dioxo-1,3-diallyl-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl]oxy]acetamide
AS94	1,3-di-n-propyl-8-{5-[(4-(ethoxycarbonyl)-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine
AS103	1,3-di-n-propyl-8-(2-hydroxypyridin-5-yl)-xanthine
AS105	1,3-diallyl-8-{5-[2-oxo-2-(4-(pyridin-2-yl)-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine
AS106	1,3-diallyl-8-{5-[2-oxo-2-(4-(pyrimidin-2-yl)-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine
AS109	1,3-di-n-propyl-8-{5-[(4-(aminosulfonyl)phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

## Synthesis of Compounds

[62] The compounds of the present invention may be synthesized by any suitable means. However, the 8-heteroaryl-xanthine derivatives of the present invention are preferably synthesized by condensation of a suitably substituted heteroaryl-carboxylic acid with a 1,3-disubstituted-5,6-diaminouracil to form an amide, which is subsequently cyclized to give a 1,3-disubstituted-8-heteroaryl-xanthine.

[63] If desired, reaction of this product under conditions commonly employed by one skilled in the art would provide additional compounds of

the present invention. For example, 1,3-disubstituted-8-heteroaryl-xanthines containing a primary amine on the heteroaryl moiety could be further reacted with an appropriate carboxylic acid, acid halide, carboxylic acid ester, or isocyanate under conditions widely known to those skilled in the art to provide the corresponding amides or ureas of the present invention.

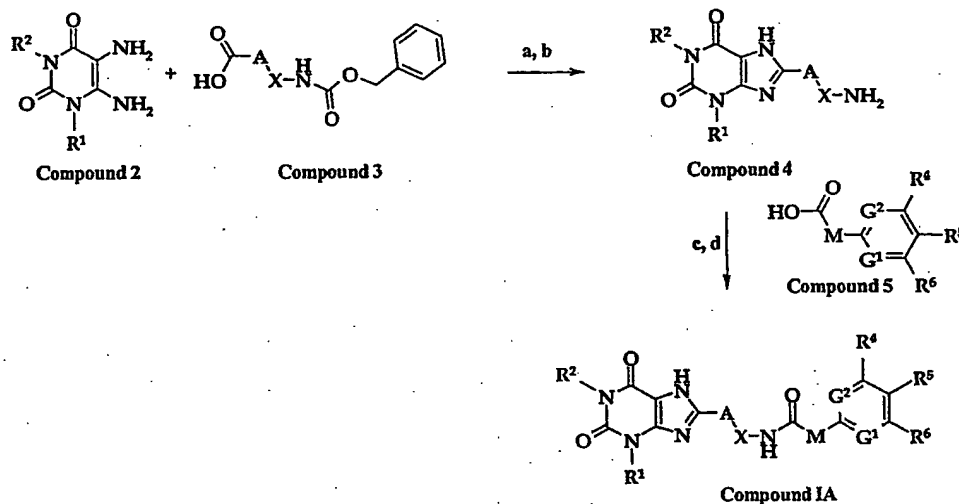
[64] Similarly, the 1,3-disubstituted-8-heteroaryl-xanthines containing a hydroxyl group attached to the heteroaryl moiety might be reacted with a suitable acyl ester, acid halide,  $\alpha$ -halocarbonyl compound, isocyanate, sulfinyl halide or sulfonyl halide to afford the respective ester,  $\beta$ -oxycarbonyl compound, carbamate, sulfinate, or sulfonate. A further example can be seen in which a 1,3-disubstituted-8-heteroaryl-xanthine containing a carboxylic acid attached to the heteroaryl moiety may be reacted with an appropriate aniline, heteroarylamine, alkylamine, or aralkylamine to afford the corresponding amide.

[65] It will be recognized by one skilled in the art that numerous other possibilities are conceivable in the substituent attached to the heteroaryl moiety and the functional group it is reacted with. It will also be recognized that the suggested additional reactions are not exhaustive, but merely illustrative.

[66] In general, the compounds of the present invention are prepared as depicted in the accompanying schemes. As shown in **Scheme 1**, a 1,3-disubstituted-5,6-diaminouracil (**Compound 2**) may be dissolved in an appropriate volume of a lower alcohol with an appropriate heteroaryl carboxylic acid (**Compound 3**) and a suitable coupling agent, such as 3-ethyl-1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) or 1,3-dicyclohexylcarbodiimide (DCC), at a temperature of 5 to 70 °C, for a period of 1 to 24 hours.

[67] After removing the residual solvent, the intermediate amide is treated with an excess of an aqueous basic solution, such as sodium hydroxide or potassium hydroxide at a temperature of 30 to 100 °C for 1 to 12 hours to

afford the desired 8-(aminoheteroaryl)-1,3-disubstituted-xanthine  
(Compound 4).

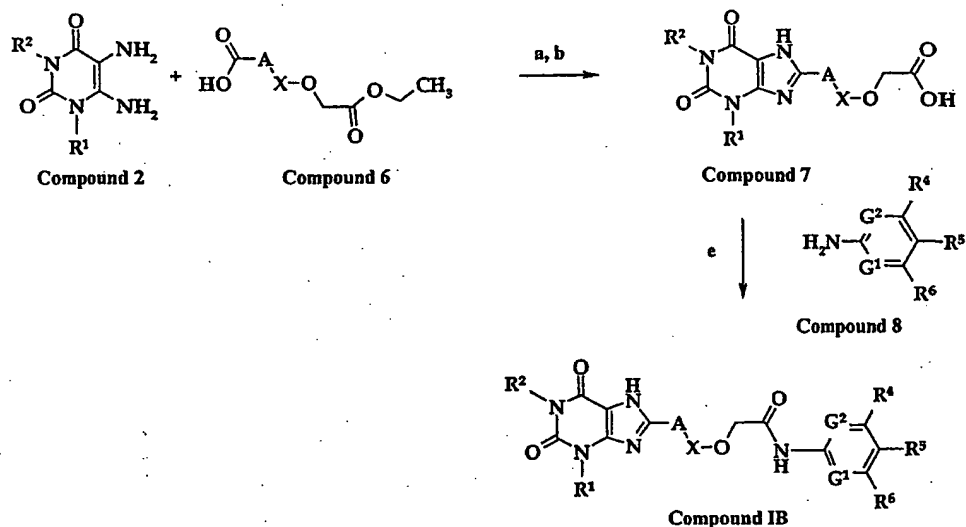


Scheme 1: a) EDCI. b) NaOH. c) SOCl<sub>2</sub>. d) TEA, CH<sub>2</sub>Cl<sub>2</sub>

[68] After cooling the resulting clear aqueous solution to room temperature, the solution is typically acidified to approximately pH = 5 using a suitable inorganic acid, such as concentrated HCl, until the intermediate 8-(aminoheteroaryl)-1,3-disubstituted-xanthine precipitates. The precipitated intermediate may then be collected by filtration or centrifugation further purifying, if desired, by recrystallization from an appropriate solvent or combination of solvents or by chromatography.

[69] A solution of the requisite carboxylic acid (Compound 5) may then be converted to the corresponding acyl halide by suspending in the appropriate halogenating reagent, such as thionyl chloride, phosphorus oxychloride, thionyl bromide, phosphorus trichloride, or phosphorus tribromide, optionally in the presence of a suitable solvent, such as methylene chloride, chloroform, 1,2-dichloroethane, 1,4-dioxane, or diethyl ether, and warming to between 30 and 90 °C for 1 to 18 hours.

- [70] After removal of the excess halogenating reagent, a solution of the intermediate 8-(aminoheteroaryl)-1,3-disubstituted-xanthine and a suitable base, such as triethylamine, diethylisopropylamine, or diisopropylethylamine, is added to the acyl halide dissolved in an appropriate solvent. After stirring the mixture at 10 to 80 °C for 1 to 36 hours, the mixture is evaporated, and the residue partitioned between an organic solvent and a saturated aqueous solution of sodium bicarbonate. After drying the organic extract, the desired product is typically purified by column chromatography on silica gel.
- [71] Alternatively, compounds of the present invention may be prepared as depicted in **Scheme 2**. In this sequence, 1,3-disubstituted-5,6-diaminouracils (**Compound 2**) may be condensed with heteroarylcarboxylic acids possessing an ethoxycarbonylmethoxy group attached to the heteroaryl moiety. Such condensation may be effected by treating a solution of the 1,3-disubstituted-5,6-diaminouracil (**Compound 2**) in an appropriate volume of a lower alcohol with the desired heteroaryl carboxylic acid (**Compound 6**) and a suitable coupling agent, such as 3-ethyl-1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) or 1,3-dicyclohexylcarbodiimide (DCC), at a temperature of 5 to 70 °C, for a period of 1 to 24 hours.
- [72] After removing the residual solvent, the intermediate amide is treated with an excess of an aqueous basic solution, such as sodium hydroxide or potassium hydroxide at a temperature of 30 to 100 °C for 15 minutes to 12 hours to afford the desired 8-(carboxymethoxy-heteroaryl)-1,3-disubstituted-xanthine (**Compound 7**).



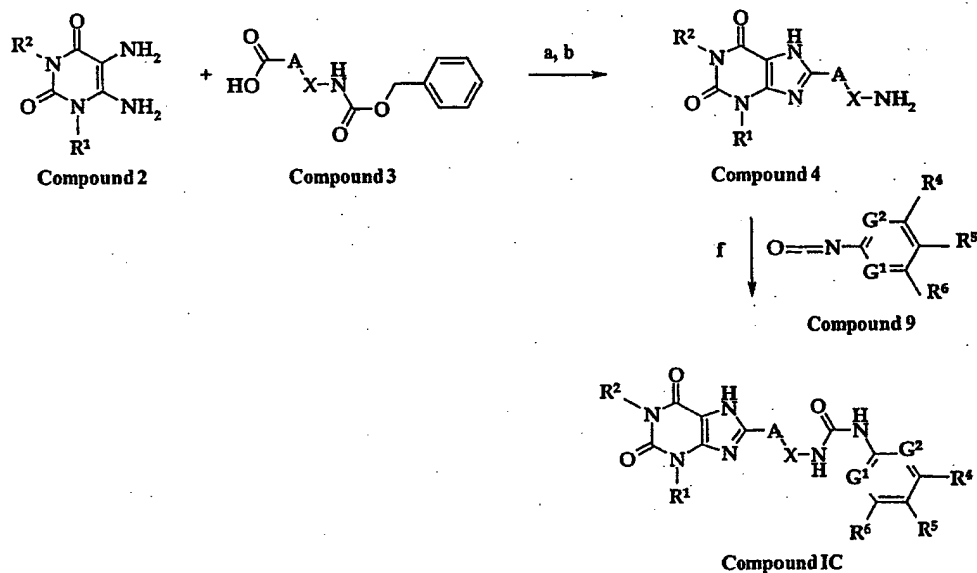
Scheme 2: a) EDCI. b) NaOH. e) EDCI, HOBt, DMF

[73] Condensation of the intermediate xanthine (Compound 7) with a suitable aniline, or heteroaromatic amine (Compound 8) affords the desired products following normal purification procedures. This condensation is typically performed in dimethylformamide, or other suitable solvent, such as dimethylacetamide, hexamethylphosphortriamide, or ethyl acetate, using EDCI and HOBt to promote the amide bond formation at temperatures of 10 to 90 °C for periods of 10 minutes to 24 hours.

[74] It will be recognized that a variety of other condensation procedures, all well known in the art, such as the use of DCC or the conversion of the carboxylic acid to an activated ester and displacement with the amine, will also result in the preparation of the desired compounds.

[75] In another illustrative synthesis example, Scheme 3, the intermediate Compound 4, dissolved in an appropriate solvent such as anhydrous 1,4-dioxane, methylene chloride, 1,2-dichloroethane, or 1,2-dimethoxyethane, is treated with a suitable isocyanate (Compound 9) at room temperature

or above for a period of 4 to 24 hours to afford the desired 8-heteroaryl)xanthine ureas. The desired products are typically precipitated by the addition of water, followed by column chromatography purification on silica gel.



**Scheme 3:** a) EDCI. b) NaOH. f) 1,4-dioxane

[76] 5,6-Diamino-1,3-dimethyluracil, 5,6-diamino-1,3-diallyluracil, and 5,6-diamino-1,3-diisobutyluracil are commercially available. The 5,6-diamino-1,3-diisobutyluracil may be prepared as previously described (M. Merlos, et al., *Eur. J. Med. Chem.* **25**: 652 (1990)). The synthesis of 1-methyl-3-benzyloxy-carbonylamino-pyrazole-5-carboxylic acid and 1-methyl-5-benzyloxycarbonylamino-pyrazole-3-carboxylic acid follows the method of Lee and Cain (*J. Org. Chem.* **54**: 428 (1989)).

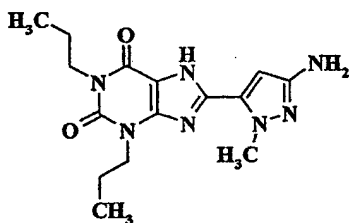
[77] The synthesis of ethyl (3-carboxy-1-methylpyrazol-5-yl)oxyacetic acid and ethyl (5-carboxy-1-methylpyrazol-3-yl)oxyacetic acid has been described by Sucrow and coworkers (*Chem. Ber.* **109**: 253 (1976) and *Chem. Ber.* **109**: 268 (1976)). 1-Methyl-4-nitroimidazole-2-carboxylate is prepared as described by Krowicki and Lown (*J. Org. Chem.* **52**: 3493

(1987)). 1-Methyl-4-nitropyrrole-2-carboxylate is commercially available. Aicher and coworkers (*J. Med. Chem.* 41: 4556 (1998)) recently described the preparation of 3-substituted-5-hydroxymethyl-isoxazoles, which are readily acylated using methods well known to those skilled in the art.

[78] The 4-(substituted)-benzyloxyphenylacetic acids not commercially available may be prepared from methyl 4-hydroxyphenylacetate and the appropriate benzyl halides, as described by Müller, Reindl, and Breu (*J. Med. Chem.* 44: 814 (2001)) for 4-(3-methoxybenzyloxy)phenylacetic acid. All other starting materials are generally available from normal commercial sources.

[79] The following examples are provided in a non-limiting manner to further illustrate the methods of synthesis and use of the compounds of the present invention.

### Example 1 - Preparation of Compound AS3



[80] A solution of 1,3-dipropyl-5,6-diaminouracil (0.7 g, 0.003 mol), 1-methyl-3-(benzyloxycarbonylamino)-pyrazole-5-carboxylic acid (0.8 g, 0.003 mol), and EDCI (0.6 g, 0.003 mol) in 50 mL of CH<sub>3</sub>OH was stirred at room temperature for two hours. Excess CH<sub>3</sub>OH was evaporated in vacuo to give a yellow solid that was collected by filtration and washed with H<sub>2</sub>O to give the amide intermediate.

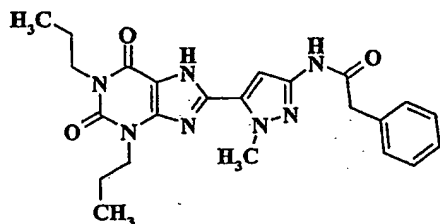
[81] A mixture of the amide intermediate and 30 mL of 2.5 N NaOH was warmed to 70-80 °C for three hours. The clear aqueous solution was cooled and acidified to pH 5 with concentrated HCl. The white precipitate that formed was collected by filtration and washed with H<sub>2</sub>O to afford the



desired 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine, which was recrystallized from CH<sub>3</sub>OH.

[82] MP: 285-288 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.93 (m, 6H), 1.58 (m, 2H), 1.75 (m, 2H), 3.88 (bs, 2H), 4.01 (s, 5H), 6.21 (s, 1H), 13.51 (bs, 1H).

### Example 2 - Preparation of Compound AS11

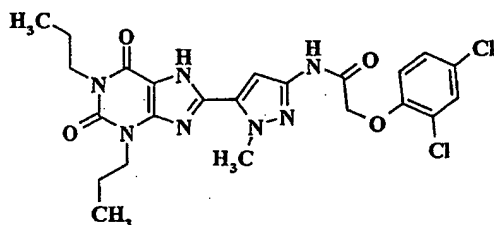


[83] A solution of phenylacetic acid (0.196 mmol) in 3 mL of thionyl chloride was stirred at 70 °C for four hours, then excess thionyl chloride removed in a nitrogen stream. A solution of 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (0.151 mmol, Example 1) and 0.04 mL of anhydrous triethylamine in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>: CH<sub>3</sub>OH (1:1) was added and the mixture was stirred at room temperature for 24 hours, monitoring by TLC.

[84] At completion, the solvent was evaporated, the residue dissolved in ethyl acetate, and the solution washed with saturated aqueous NaHCO<sub>3</sub> and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated *in vacuo*. The desired product was purified by column chromatography on silica gel.

[85] MP: 139-140 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.89 (q, 6H, J = 5.18 Hz), 1.59 (q, 2H, J = 7.18 Hz), 1.72 (q, 2H, J = 7.06 Hz), 3.62 (s, 2H), 3.88 (t, 2H, J = 6.72 Hz), 3.98 (t, 2H, J = 6.96 Hz), 4.12 (s, 3H), 7.25 – 7.33 (m, 6H), 10.8 (s, 1H), 14.02 (s, 1H).

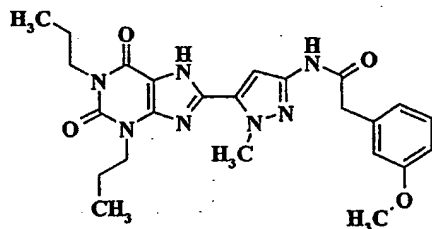
### Example 3 - Preparation of Compound AS12



[86] Using 2,4-dichlorophenoxyacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[87] MP: 225-226 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.85 (m, 6H), 1.59 (m, 2H), 1.72 (m, 2H), 3.85 (t, 2H), 4.01 (t, 2H), 4.14 (s, 3H), 4.87 (s, 2H), 7.10 (d, 1H), 7.33 (m, 2H), 7.60 (d, 1H), 10.80 (s, 1H), 14.02 (s, 1H).

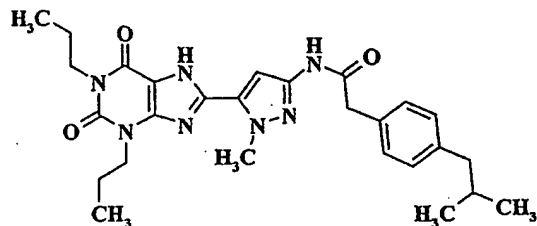
### Example 4 - Preparation of Compound AS13



[88] Using 3-methoxyphenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[89] MP: 158-159 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.89 (q, 6H, J = 7.13 Hz), 1.62 (q, 2H), 1.72 (q, 2H), 3.59 (s, 2H), 3.74 (s, 3H), 3.85 (t, 2H), 4.00 (t, 2H), 4.13 (s, 3H), 6.92 (s, 1H), 7.30 (m, 4H), 10.77 (s, 1H), 14.00 (s, 1H).

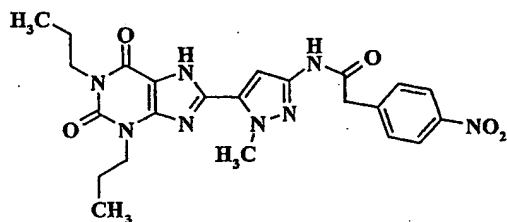
### Example 5 - Preparation of Compound AS14



[90] Using 4-(2-methylpropyl)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[91] MP: 124-126 °C;  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  0.85 (m, 12H,  $J = 6.52$  Hz), 1.39 (d, 2H,  $J = 6.87$  Hz), 1.75 (m, 5H), 2.41 (d, 2H,  $J = 7.1$  Hz), 3.85 (t, 2H,  $J = 6.94$  Hz), 4.00 (t, 2H), 4.10 (s, 3H), 7.11 (d, 1H), 7.30 (m, 4H,  $J = 8.05$  Hz), 10.70 (s, 1H), 13.99 (s, 1H).

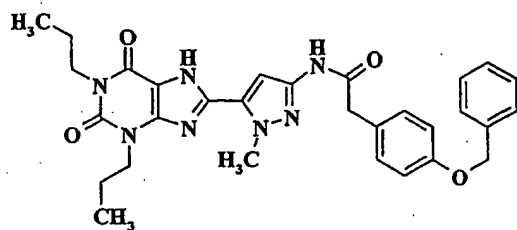
### Example 6 - Preparation of Compound AS15



[92] Using 4-nitrophenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[93] MP: 285-287 °C;  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  0.89 (m, 6H,  $J = 6.83$  Hz), 1.55 (q, 2H,  $J = 6.83$  Hz), 1.72 (q, 2H,  $J = 7.05$  Hz), 3.89 (d, 4H), 4.00 (t, 2H), 4.13 (s, 3H), 7.27 (s, 1H), 7.63 (d, 2H,  $J = 8.47$  Hz), 8.18 (d, 2H,  $J = 8.34$  Hz), 10.87 (s, 1H), 13.90 (s, 1H).

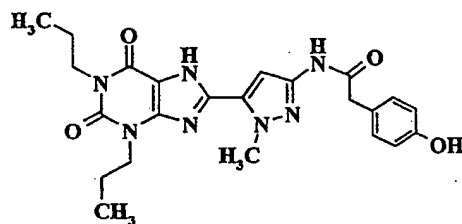
### Example 7 - Preparation of Compound AS16



[94] Using 4-(benzyloxy)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[95] MP: 184-185 °C;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  0.89 (m, 6H), 1.59 (q, 2H,  $J$  = 6.98 Hz), 1.69 (q, 2H,  $J$  = 7.1 Hz), 3.54 (s, 2H), 3.85 (t, 2H), 3.98 (t, 2H), 4.13 (s, 3H), 5.00 (s, 2H), 6.98 (d, 1H), 7.28 (m, 9H,  $J$  = 6.46 Hz), 10.75 (s, 1H), 14.02 (s, 1H).

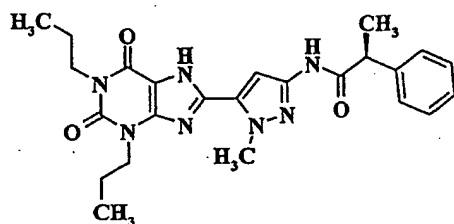
### Example 8 - Preparation of Compound AS17



[96] Using 4-hydroxyphenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[97] MP: 145-150 °C;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  0.86 (m, 6H), 1.55 (m, 2H), 1.72 (m, 2H), 3.40 (s, 2H), 3.85 (t, 2H), 3.98 (t, 2H), 4.10 (s, 3H), 6.69 (d, 2H,  $J$  = 8), 7.12 (d, 2H,  $J$  = 8), 7.31 (s, 1H), 9.20 (s, 1H), 10.70 (s, 1H), 14.0 (s, 1H).

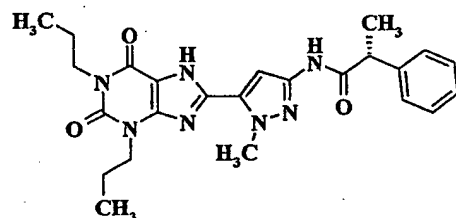
### Example 9 - Preparation of Compound AS18



[98] Using (S)-2-phenylpropanoic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[99] MP: 125-126 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 0.85 (m, 6H), 1.57 (s, 3H), 1.59 (m, 2H), 1.61 (m, 2H), 1.70 (m, 1H), 4.1 (m, 4H), 4.16 (s, 3H), 7.37 (m, 5H), 7.39 (s, 1H), 7.90 (s, 1H), 12.8 (s, 1H).

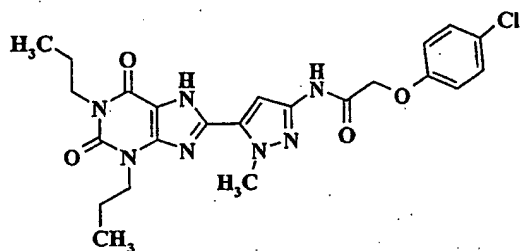
### Example 10 - Preparation of Compound AS19



[100] Using (R)-2-phenylpropanoic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[101] MP: 125-126 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 0.85 (m, 6H), 1.57 (s, 3H), 1.59 (m, 2H), 1.61 (m, 2H), 1.70 (m, 1H), 4.1 (m, 4H), 4.16 (s, 3H), 7.37 (m, 5H), 7.39 (s, 1H), 7.90 (s, 1H), 12.8 (s, 1H).

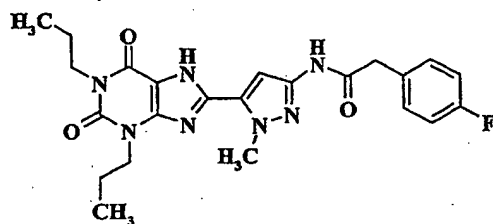
### Example 11 - Preparation of Compound AS21



**[102]** Using 4-chlorophenoxyacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[103]** MP: 260-261 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.85 (m, 6H), 1.59 (m, 2H), 1.72 (m, 2H), 3.85 (t, 2H), 3.98 (t, 2H), 4.14 (s, 3H), 6.98 (d, 2H, J = 8.0Hz), 7.36 (d, 2H, J = 8.0Hz), 7.33 (s, 1H), 10.80 (s, 1H), 14.02 (s, 1H).

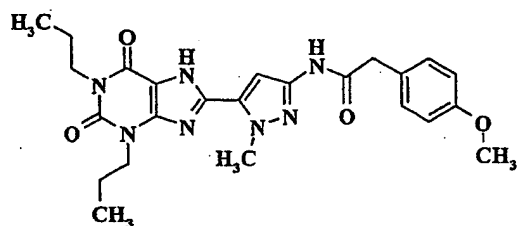
### Example 12 - Preparation of Compound AS22



**[104]** Using 4-fluorophenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[105]** MP: 176 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.60 (m, 2H), 1.70 (m, 2H), 3.60 (s, 2H), 3.70 (s, 3H), 3.80 (t, 2H), 4.00 (t, 2H), 4.10 (s, 3H), 7.15 (m, 2H), 7.31 (m, 2H), 7.30 (s, 1H), 10.70 (s, 1H), 14.0 (s, 1H).

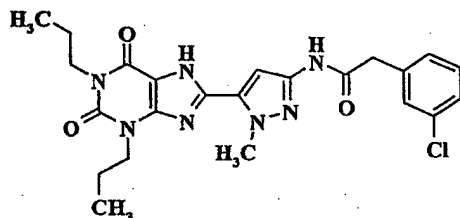
### Example 13 - Preparation of Compound AS23



**[106]** Using 4-methoxyphenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[107]** MP: 125-126 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.86 (m, 6H), 1.50 (m, 2H), 1.70 (m, 2H), 3.50 (s, 2H), 3.70 (s, 3H), 3.80 (t, 2H), 4.00 (t, 2H), 4.10 (s, 3H), 7.15 (m, 2H), 7.31 (m, 2H), 7.30 (s, 1H), 10.70 (s, 1H), 14.0 (s, 1H).

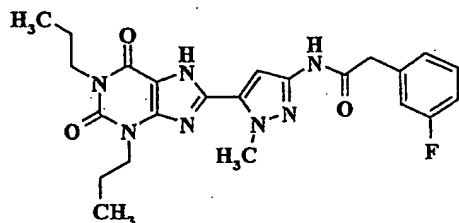
### Example 14 - Preparation of Compound AS24



**[108]** Using 3-chlorophenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[109]** MP: 143-145 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.86 (m, 6H), 1.50 (m, 2H), 1.70 (m, 2H), 3.60 (s, 2H), 3.80 (t, 2H), 4.00 (t, 2H), 4.10 (s, 3H), 7.30 (m, 4H), 7.40 (s, 1H), 10.8 (s, 1H), 14.0 (s, 1H).

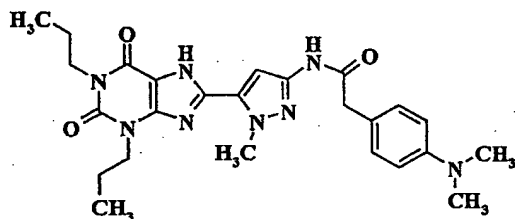
### Example 15 - Preparation of Compound AS25



**[110]** Using 3-fluorophenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[111]** MP: 148-150 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.86 (m, 6H), 1.50 (m, 2H), 1.70 (m, 2H), 3.60 (s, 2H), 3.80 (t, 2H), 4.00 (t, 2H), 4.10 (s, 3H), 7.10 (m, 4H), 7.30 (s, 1H), 10.8 (s, 1H), 14.0 (s, 1H).

### Example 16 - Preparation of Compound AS26

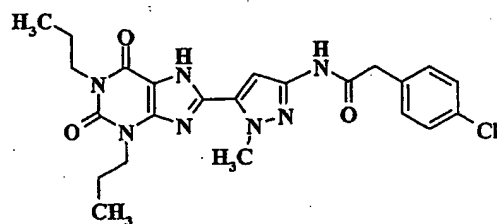


**[112]** Using 4-(dimethylamino)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[113]** MP: 215 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.86 (m, 6H), 1.50 (m, 2H), 1.70 (m, 2H), 2.80 (s, 6H), 3.60 (s, 2H), 3.80 (t, 2H), 4.00 (t, 2H), 4.10 (s, 3H), 6.67 (d, 2H, J = 8.0Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.29 (s, 1H), 10.8 (s, 1H), 14.0 (s, 1H).



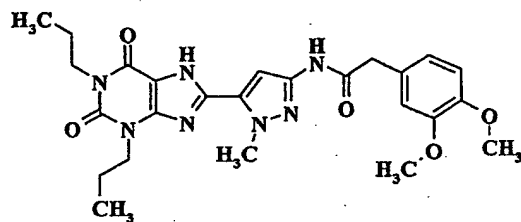
### Example 17 - Preparation of Compound AS27



[114] Using 4-chlorophenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[115] MP: 159-161 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.86 (m, 6H), 1.50 (m, 2H), 1.70 (m, 2H), 3.60 (s, 2H), 3.80 (t, 2H), 4.00 (t, 2H), 4.10 (s, 3H), 7.29 (s, 1H), 7.32 (d, 2H, J = 8.0Hz), 7.38 (d, 2H, J = 8.0 Hz), 10.8 (s, 1H), 14.0 (s, 1H).

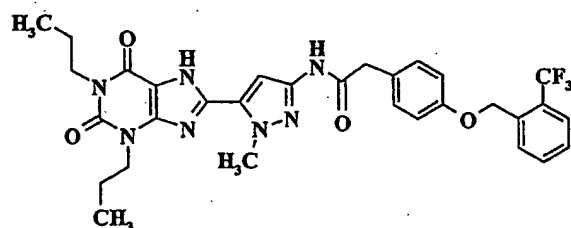
### Example 18 - Preparation of Compound AS28



[116] Using 3,4-(dimethoxy)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[117] MP: 140-142 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H), 1.55 (q, 2H), 1.72 (q, 2H), 3.50 (s, 2H), 3.74 (s, 6H), 3.82 (t, 2H), 4.02 (t, 2H), 4.13 (s, 3H), 6.88 (m, 3H, J = 3.58), 6.96 (d, 1H), 7.33 (s, 1H), 10.73 (s, 1H).

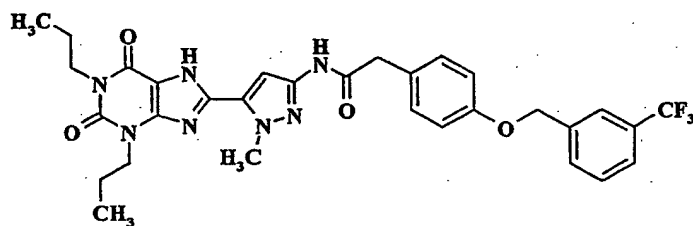
### Example 19 - Preparation of Compound AS29



**[118]** Using 4-(2-trifluoromethylbenzyloxy)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[119]** MP: 184-186 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.59 (q, 2H), 1.69 (q, 2H), 3.54 (s, 2H), 3.85 (t, 2H), 4.00 (t, 2H), 4.12 (s, 3H), 5.20 (s, 2H), 6.92 (d, 1H), 7.28 (m, 3H, J = 5.48), 7.73 (m, 4H, J = 6.55), 10.75 (s, 1H), 14.02 (s, 1H).

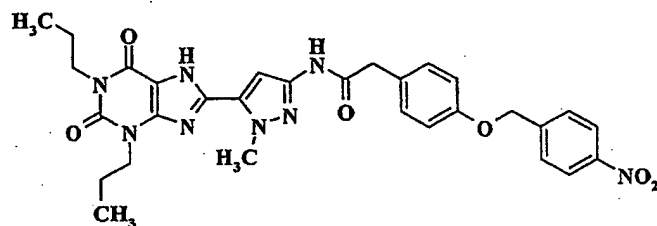
### Example 20 - Preparation of Compound AS30



**[120]** Using 4-(3-trifluoromethylbenzyloxy)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[121]** MP: 218-220 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H, J = 5.06), 1.55 (q, 2H, J = 6.88), 1.72 (q, 2H, J = 7.47), 3.55 (s, 2H), 4.01 (t, 2H), 4.08 (t, 2H), 4.12 (s, 3H), 5.20 (s, 2H), 5.76 (s, 1H), 7.00 (d, 1H), 7.68 (t, 3H), 7.80 (m, 4H), 10.75 (s, 1H), 14.01 (s, 1H).

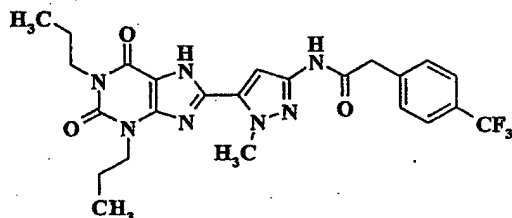
### Example 21 - Preparation of Compound AS31



[122] Using 4-(4-nitrobenzyloxy)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[123] MP: 136-139 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.55 (q, 2H), 1.72 (q, 2H), 3.55 (s, 2H), 4.01 (t, 2H), 4.08 (t, 2H), 4.12 (s, 3H), 5.20 (s, 2H), 7.00 (d, 1H), 7.48 (t, 4H), 7.80 (d, 2H), 8.30 (d, 2H), 10.75 (s, 1H).

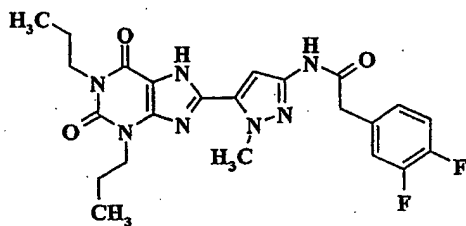
### Example 22 - Preparation of Compound AS32



[124] Using 4-(trifluoromethyl)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[125] MP: 240 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.55 (q, 2H), 1.72 (q, 2H), 3.75 (s, 2H), 3.89 (t, 2H), 4.01 (t, 2H), 4.08 (s, 3H), 7.27 (s, 1H), 7.68 (d, 2H), 7.80 (d, 2H), 10.85 (s, 1H).

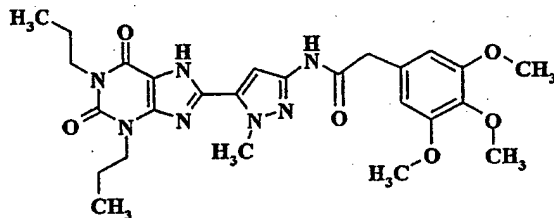
## Example 23 - Preparation of Compound AS43



[126] Using 3,4-difluorophenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[127] MP: 250-252 °C;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  0.86 (m, 6H), 1.50 (m, 2H), 1.70 (m, 2H), 3.60 (s, 2H), 3.80 (t, 2H), 4.00 (t, 2H), 4.10 (s, 3H), 7.29 (s, 1H), 7.32 (m, 3H), 10.80 (s, 1H), 14.00 (s, 1H).

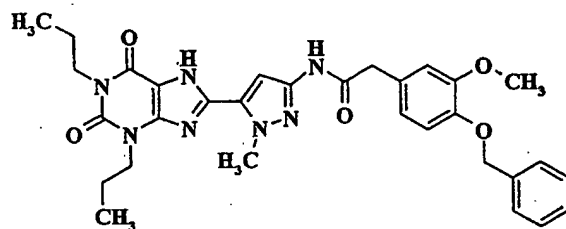
## Example 24 - Preparation of Compound AS44



[128] Using 3,4,5-(trimethoxy)phenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[129] MP: 298-300 °C;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  0.88 (m, 6H), 1.55 (q, 2H), 1.72 (q, 2H), 3.54 (s, 2H), 3.62 (s, 3H), 3.75 (s, 6H), 3.85 (t, 2H), 4.01 (t, 2H), 4.13 (s, 3H), 6.66 (s, 2H), 7.33 (s, 1H), 10.74 (s, 1H), 14.01 (s, 1H).

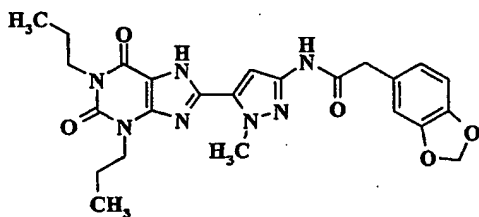
## Example 25 - Preparation of Compound AS56



**[130]** Using 4-(benzyloxy)-3-methoxyphenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[131]** MP: 205-208 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.89 (m, 6H), 1.55 (m, 2H), 1.72 (m, 2H), 3.54 (s, 2H), 3.76 (s, 3H), 3.85 (t, 2H), 4.01 (t, 2H), 4.13 (s, 3H), 5.04 (s, 2H), 6.84 (d, 1H), 6.98 (d, 2H), 7.38 (m, 6H, J = 8.36), 10.72 (s, 1H).

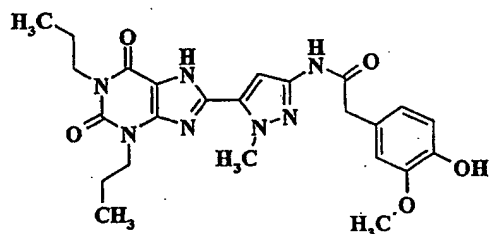
## Example 26 - Preparation of Compound AS57



**[132]** Using 3,4-methylenedioxyphenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

**[133]** MP: 138-140 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.58 (m, 2H), 1.71 (m, 2H), 3.52 (s, 2H), 3.85 (t, 2H), 4.00 (t, 2H), 4.12 (s, 3H), 5.97 (s, 2H), 6.83 (m, 3H), 7.27 (s, 1H), 10.71 (s, 1H), 14.00 (s, 1H).

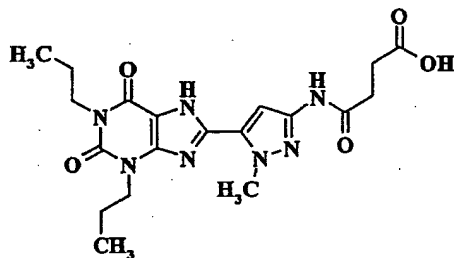
### Example 27 - Preparation of Compound AS58



[134] Using 4-hydroxy-3-methoxyphenylacetic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[135] MP: 185 °C;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  0.88 (m, 6H), 1.58 (m, 2H), 1.71 (m, 2H), 3.40 (s, 2H), 3.81 (s, 3H), 3.83 (t, 2H), 3.88 (t, 2H), 4.12 (s, 3H), 6.70 (s, 2H), 6.90 (s, 1H), 7.30 (s, 1H), 8.80 (s, 1H), 10.71 (s, 1H), 14.00 (s, 1H).

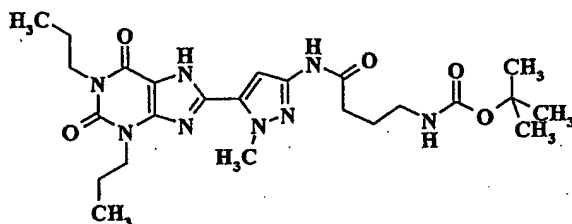
### Example 28 - Preparation of Compound AS8



[136] A solution of succinic anhydride and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3) in 1,4-dioxane was heated at 60 °C overnight, the solvent removed, and the residue purified by column chromatography on silica gel to provide the desired product.

[137] MP: 265-266 °C;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  0.86 (m, 6H), 1.55 (m, 2H), 1.72 (m, 2H), 3.31 (s, 2H), 3.34 (s, 2H), 3.65 (t, 2H), 3.98 (t, 2H), 4.01 (s, 3H), 7.33 (s, 1H), 10.50 (s, 1H), 12.10 (s, 1H), 14.01 (s, 1H).

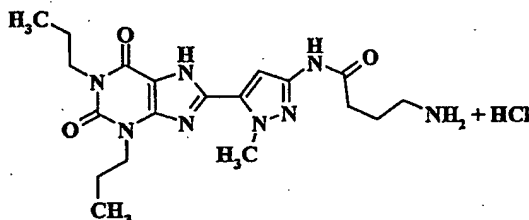
### Example 29 - Preparation of Compound AS9



[138] Using 4-(t-butyloxycarbonylamino)butanoic acid and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[139] MP: 215-216 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.89 (m, 6H), 1.37 (s, 9H), 1.66 (m, 6H), 2.28 (m, 2H), 2.91 (m, 2H), 3.86 (t, 2H), 4.01 (t, 2H), 4.12 (s, 3H), 7.30 (s, 1H), 10.50 (s, 1H), 14.01 (s, 1H).

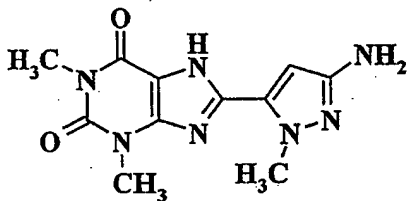
### Example 30 - Preparation of Compound AS10



[140] A solution of 1,3-dipropyl-8-(3-(4-(t-butyloxycarbonylamino)-1-oxo-butylamino)-1-methyl-pyrazol-5-yl)xanthine (Example 29) in 1,4-dioxane was treated with excess ethereal HCl (2 N) at room temperature for 16 hours, during which a white solid precipitated. This was collected by filtration, washing with diethyl ether to afford the desired product as the hydrochloride salt.

[141] MP: 251-252 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.89 (m, 6H), 1.59 (m, 2H), 1.72 (m, 4H), 2.45 (m, 2H), 2.81 (t, 2H), 3.86 (t, 2H), 3.98 (t, 2H), 4.12 (s, 3H), 7.30 (s, 1H), 7.95 (s, 3H), 10.62 (s, 1H), 14.02 (s, 1H).

## Example 31 - Preparation of Compound AS38

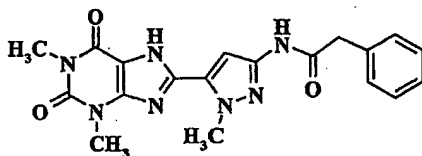


[142] A solution of 1,3-dimethyl-5,6-diaminouracil (0.7 g, 0.003 mol), 1-methyl-3-(benzyloxycarbonylamino)-pyrazole-5-carboxylic acid (0.8 g, 0.003 mol), and EDCI (0.6 g, 0.003 mol) in 50 mL of CH<sub>3</sub>OH was stirred at room temperature for two hours. Excess CH<sub>3</sub>OH was evaporated in vacuo to give a yellow solid that was collected by filtration and washed with H<sub>2</sub>O to give the amide intermediate.

[143] A mixture of the amide intermediate and 30 mL of 2.5 N NaOH was warmed to 70-80 °C for three hours. The clear aqueous solution was cooled and acidified to pH 5 with concentrated HCl. The white precipitate that formed was collected by filtration and washed with H<sub>2</sub>O to afford the desired 1,3-dimethyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine, which was recrystallized from CH<sub>3</sub>OH.

[144] MP: >300 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 3.20 (s, 3H), 3.40 (s, 3H), 4.00 (s, 3H), 5.50 (s, 2H), 6.20 (s, 1H), 13.20 (s, 1H).

## Example 32 - Preparation of Compound AS40



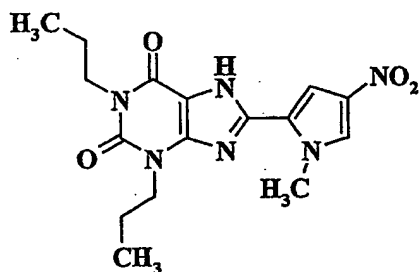
[145] Using phenylacetic acid and 1,3-dimethyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 31).

[146] MP: >300 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 3.20 (s, 3H), 3.40 (s, 3H), 3.60 (s,



2H), 4.10 (s, 3H), 7.30 (s, 1H), 7.40 (m, 5H), 10.80 (s, 1H), 14.00 (s, 1H).

### Example 33 - Preparation of Compound AS7

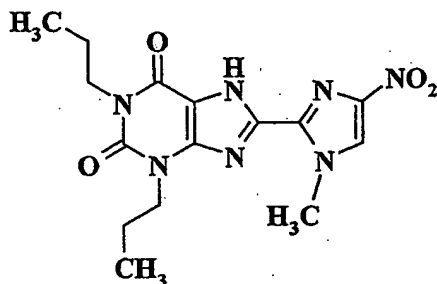


[147] A solution of 1,3-dipropyl-5,6-diaminouracil (0.7 g, 0.003 mol), 1-methyl-4-nitropyrrole-2-carboxylic acid (0.8 g, 0.003 mol), and EDCI (0.6 g, 0.003 mol) in 50 mL of CH<sub>3</sub>OH was stirred at room temperature for two hours. Excess CH<sub>3</sub>OH was evaporated *in vacuo* to give a yellow solid that was collected by filtration and washed with H<sub>2</sub>O to give the amide intermediate.

[148] A mixture of the amide intermediate and 30 mL of 2.5 N NaOH was warmed to 70-80 °C for three hours. The clear aqueous solution was cooled and acidified to pH 5 with concentrated HCl. The white precipitate that formed was collected by filtration and washed with H<sub>2</sub>O to afford the desired 1,3-dipropyl-8-(1-methyl-4-nitropyrrol-2-yl)xanthine, which was recrystallized from CH<sub>3</sub>OH.

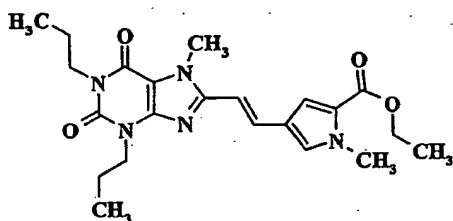
[149] MP: 295-297 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.86 (m, 6H), 1.55 (m, 2H), 1.72 (m, 2H), 3.88 (t, 2H), 3.98 (t, 2H), 3.99 (s, 3H), 7.52 (s, 1H), 8.20 (s, 1H), 14.00 (s, 1H).

## Example 34 - Preparation of Compound AS36



[150] Using 1,3-dipropyl-5,6-diaminouracil and 1-methyl-4-nitroimidazole-2-carboxylic acid.

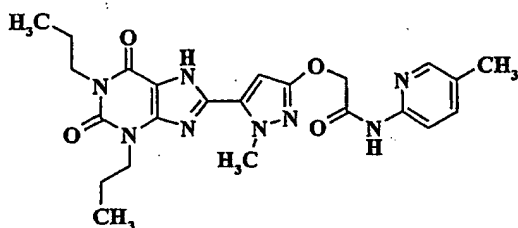
## Example 35 - Preparation of Compound AS33



[151] Using 1,3-dipropyl-5,6-diaminouracil and 3-(2-ethoxycarbonyl-1-methylpyrrol-4-yl)acrylic acid.

[152] MP: 210-211 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.85 (m, 6H), 1.30 (t, 3H), 1.59 (m, 2H), 1.72 (m, 2H), 3.85 (s, 3H), 4.03 (s, 3H), 4.10 (q, 2H), 7.10 (d, 2H), 7.59 (d, 2H), 7.60 (s, 1H).

## Example 36 - Preparation of Compound AS59

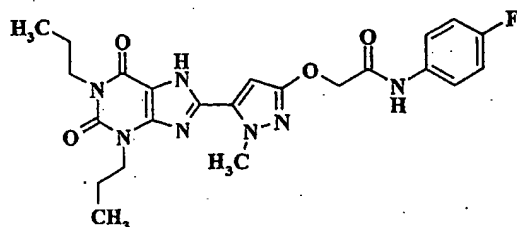


[153] To a solution of ethyl (5-carboxy-1-methylpyrazol-3-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) was added a solution of 1,3-dipropyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture was stirred at room temperature for two hours, the solvent was then removed *in vacuo*, water added, and the solid that formed was collected by filtration and washed with additional cold water. The intermediate amide was heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid.

[154] Condensation of 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (0.5 mmol) and 5-methyl-2-aminopyridine (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

[155] MP: 278-280 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.90 (m, 6H, J = 4.66 Hz), 1.55 (m, 2H, J = 7.38 Hz), 1.67 (m, 2H, J = 7.34 Hz), 2.24 (s, 3H), 3.89 (t, 2H, J = 7.34 Hz), 4.00 (t, 2H, J = 7.14 Hz), 4.05 (s, 3H), 4.82 (s, 2H), 6.44 (s, 1H), 7.64 (dd, 1H), 7.93 (d, 1H), 8.15 (d, 1H), 10.43 (s, 1H), 13.95 (bs, 1H).

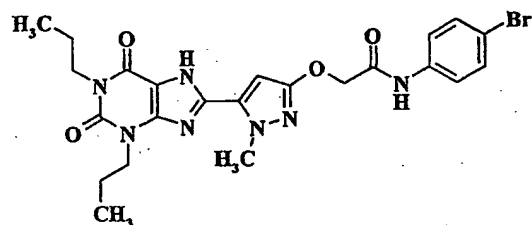
### Example 37 - Preparation of Compound AS64



[156] Using 4-fluoroaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methylpyrazol-3-yl]oxyacetic acid (Example 36).

[157] MP: 264 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H), 1.55 (q, 2H), 1.59 (q, 2H), 3.86 (t, 2H), 4.00 (t, 2H), 4.07 (s, 3H), 4.76 (s, 2H), 6.50 (s, 1H), 7.16 (m, 2H, J = 8.75Hz), 7.64 (m, 2H, J = 5.04), 10.20 (s, 1H).

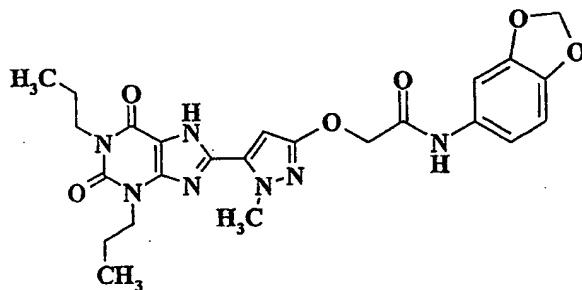
### Example 38 - Preparation of Compound AS65



[158] Using 4-bromoaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methylpyrazol-3-yl]oxyacetic acid (Example 36).

[159] MP: 264 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.90 (m, 6H), 1.59 (m, 2H), 1.71 (m, 2H), 3.86 (t, 2H), 4.00 (t, 2H), 4.06 (s, 3H), 4.77 (s, 2H), 6.50 (s, 1H), 7.52 (m, 4H), 10.26 (s, 1H).

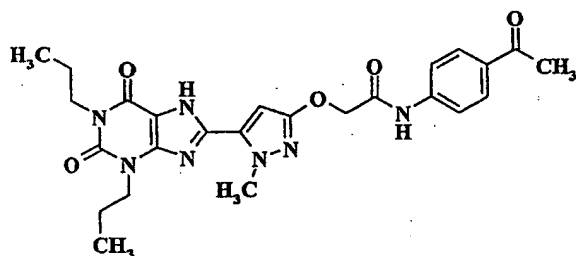
## Example 39 - Preparation of Compound AS68



[160] Using 3,4-methylenedioxyaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36).

[161] MP: 272-273 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.89 (m, 6H), 1.60 (m, 2H), 1.70 (m, 2H), 3.90 (t, 2H), 3.98 (t, 2H), 4.07 (s, 3H), 4.73 (s, 2H), 5.98 (s, 2H), 6.52 (s, 1H), 6.88 (d, 1H, J = 8.44Hz), 7.01 (d, 1H), 7.32 (s, 1H), 10.01 (s, 1H).

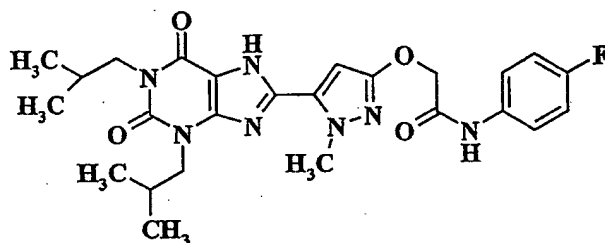
## Example 40 - Preparation of Compound AS69



[162] Using 4-acetylaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36).

[163] MP: 273-275 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.90 (m, 6H, J = 7.34Hz), 1.74 (m, 4H, J = 6.97Hz), 2.60 (s, 3H), 4.00 (bt, 2H), 4.14 (t, 2H), 4.19 (s, 3H), 4.86 (s, 2H), 6.60 (s, 1H), 7.85 (d, 2H, J = 8.58Hz), 7.96 (d, 2H, J = 8.69Hz), 8.82 (s, 1H), 12.95 (bs, 1H).

## Example 41 - Preparation of Compound AS66

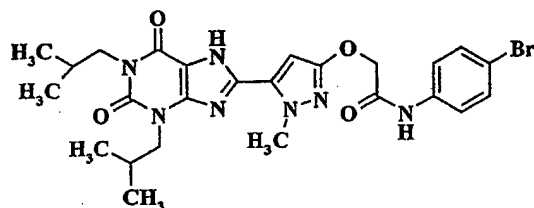


[164] To a solution of ethyl (5-carboxy-1-methylpyrazol-3-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) was added a solution of 1,3-diisobutyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture was stirred at room temperature for two hours, the solvent was then removed *in vacuo*, water added, and the solid that formed was collected by filtration and washed with additional cold water. The intermediate amide was heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 2-[5-(1,3-diisobutyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid.

[165] Condensation of 2-[5-(1,3-diisobutyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (0.5 mmol) and 4-fluoroaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

[166] MP: 227-230 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.87 (t, 12H, J = 7.58Hz), 2.05 (bm, 2H), 3.74 (d, 2H, J = 7.15Hz), 3.85 (d, 2H, J = 7.15), 4.06 (s, 2H), 4.76 (s, 2H), 6.51 (s, 1H), 7.16 (t, 2H), 7.64 (m, 2H), 10.17 (s, 1H), 13.96 (bs, 1H).

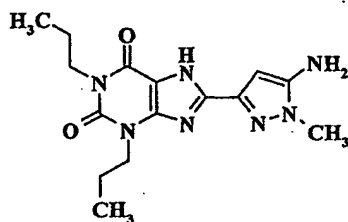
## Example 42 - Preparation of Compound AS67



[167] Condensation of 2-[5-(1,3-diisobutyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 44, Compound AS35, 0.5 mmol) and 4-bromoaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

[168] MP: 258-260 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.87 (t, 12H, J = 7.22Hz), 2.06 (m, 2H), 3.77 (d, 2H, J = 7.3Hz), 3.85 (d, 2H, J = 7.16), 4.06 (s, 3H), 4.77 (s, 2H), 6.51 (s, 1H), 7.52 (dd, 4H, J = 8.88Hz), 10.26 (s, 1H), 13.96 (s, 1H).

### Example 43 - Preparation of Compound AS37



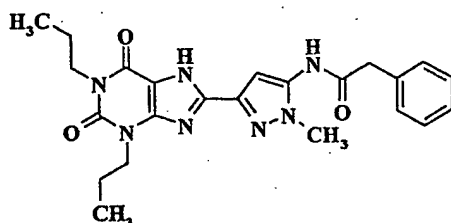
[169] A solution of 1,3-dipropyl-5,6-diaminouracil (0.7 g, 0.003 mol), 1-methyl-5-(benzyloxycarbonylamino)-pyrazole-3-carboxylic acid (0.8 g, 0.003 mol), and EDCI (0.6 g, 0.003 mol) in 50 mL of CH<sub>3</sub>OH was stirred at room temperature for two hours. Excess CH<sub>3</sub>OH was evaporated in vacuo to give a yellow solid that was collected by filtration and washed with H<sub>2</sub>O to give the amide intermediate.

[170] A mixture of the amide intermediate and 30 mL of 2.5 N NaOH was warmed to 70-80 °C for three hours. The clear aqueous solution was cooled and acidified to pH 5 with concentrated HCl. The white precipitate that formed was collected by filtration and washed with H<sub>2</sub>O to afford the desired 1,3-dipropyl-8-(5-amino-1-methylpyrazol-3-yl)xanthine, which was recrystallized from CH<sub>3</sub>OH.

[171] MP: 249-250 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.85 (m, 6H), 1.59 (m, 2H), 1.72 (m, 2H), 3.50 (s, 3H), 3.85 (m, 2H), 3.95 (m, 2H), 5.50 (d, 2H), 6.00

(s, 1H), 13.50 (s, 1H).

### Example 44 - Preparation of Compound AS35

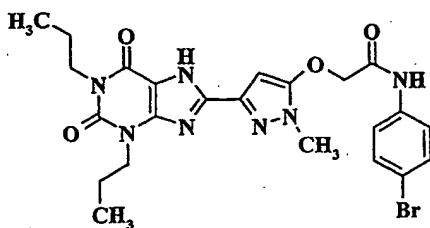


[172] A solution of phenylacetic acid (0.196 mmol) in 3 mL of thionyl chloride was stirred at 70 °C for four hours, then excess thionyl chloride removed in a nitrogen stream. A solution of 1,3-dipropyl-8-(5-amino-1-methylpyrazol-3-yl)xanthine (0.151 mmol, Example 43) and 0.04 mL of anhydrous triethylamine in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>: CH<sub>3</sub>OH (1:1) was added and the mixture was stirred at room temperature for 24 hours, monitoring by TLC.

[173] At completion, the solvent was evaporated, the residue dissolved in ethyl acetate, and the solution washed with saturated aqueous NaHCO<sub>3</sub> and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated in vacuo. The desired product was purified by column chromatography on silica gel.

[174] MP: 279-281 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.55 (m, 2H), 1.72 (m, 2H), 3.60 (s, 3H), 3.75 (s, 2H), 3.89 (t, 2H), 4.01 (t, 2H), 7.27 (s, 1H), 6.90 (s, 1H), 7.20 (m, 5H), 10.20 (s, 1H), 14.00 (s, 1H).

### Example 45 - Preparation of Compound AS60



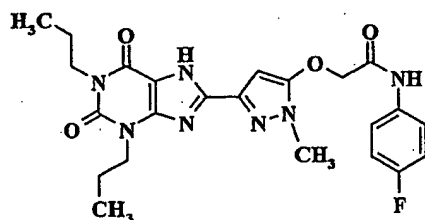


[175] To a solution of ethyl (3-carboxy-1-methylpyrazol-5-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) was added a solution of 1,3-dipropyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture was stirred at room temperature for two hours, the solvent was then removed *in vacuo*, water added, and the solid that formed was collected by filtration and washed with additional cold water. The intermediate amide was heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 3-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-5-yl]oxyacetic acid.

[176] Condensation of 3-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-5-yl]oxyacetic acid (0.5 mmol) and 4-bromoaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

[177] MP: 242 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.70 (m, 4H), 3.70 (s, 3H), 3.85 (t, 2H), 3.98 (t, 2H), 4.85 (s, 2H), 6.32 (s, 1H), 7.62 (dd, 4H, J = 8 Hz), 10.33 (s, 1H), 13.70 (s, 1H).

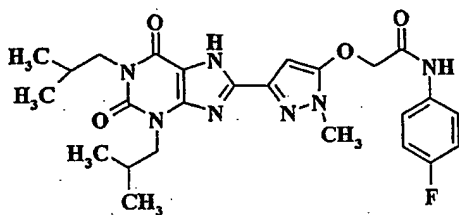
#### Example 46 - Preparation of Compound AS61



[178] Condensation of 3-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-5-yl]oxyacetic acid (Example 45, 0.5 mmol) and 4-bromoaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

[179] MP: 262 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H), 1.70 (m, 4H), 3.70 (s, 3H), 3.85 (t, 2H), 3.98 (t, 2H), 4.85 (s, 2H), 6.32 (s, 1H), 7.18 (t, 2H, J = 8.88Hz), 7.62 (m, 2H, J = 6.92 Hz), 10.25 (s, 1H), 13.70 (s, 1H).

## Example 47 - Preparation of Compound AS62

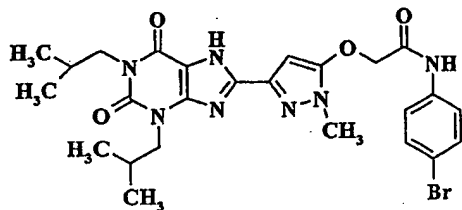


**[180]** To a solution of ethyl (3-carboxy-1-methylpyrazol-5-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) was added a solution of 1,3-diisobutyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture was stirred at room temperature for two hours, the solvent was then removed *in vacuo*, water added, and the solid that formed was collected by filtration and washed with additional cold water. The intermediate amide was heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 3-[5-(1,3-diisobutyl-xanthin-8-yl)-1-methyl-pyrazol-5-yl]oxyacetic acid.

**[181]** Condensation of 3-[5-(1,3-bisobutyl-xanthin-8-yl)-1-methyl-pyrazol-5-yl]oxyacetic acid (0.5 mmol) and 4-fluoroaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

**[182]** MP: 251-252 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.85 (t, 12H), 2.10 (m, 2H), 3.75 (s, 3H), 3.83 (dd, 4H), 4.86 (s, 2H), 6.32 (s, 1H), 7.18 (t, 2H, J = 8.85 Hz), 7.62 (m, 2H, J = 5.03 Hz), 13.70 (s, 1H).

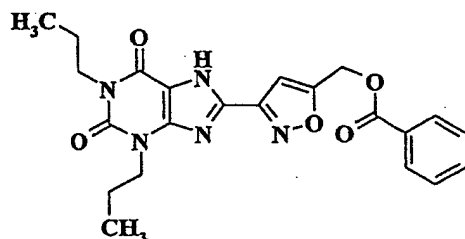
## Example 48 - Preparation of Compound AS63



[183] Condensation of 3-[5-(1,3-bisisobutyl-xanthin-8-yl)-1-methyl-pyrazol-5-yl]oxyacetic acid (xanthine intermediate from Example 47, 0.5 mmol) and 4-bromoaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBT (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

[184] MP: 234 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.84 (t, 12H), 2.10 (m, 2H), 3.73 (s, 3H), 3.831 (dd, 4H), 4.85 (s, 2H), 6.26 (s, 1H), 7.53 (q, 4H), 10.36 (s, 1H), 13.64 (s, 1H).

#### Example 49 - Preparation of Compound AS4



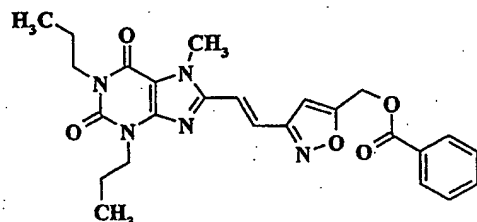
[185] A solution of 1,3-dipropyl-5,6-diaminouracil (0.7 g, 0.003 mol), 3-(benzoyloxymethyl)-oxazole-5-carboxylic acid (0.8 g, 0.003 mol), and EDCI (0.6 g, 0.003 mol) in 50 mL of CH<sub>3</sub>OH was stirred at room temperature for two hours. Excess CH<sub>3</sub>OH was evaporated *in vacuo* to give a solid that was collected by filtration and washed with H<sub>2</sub>O to afford the amide intermediate.

[186] A mixture of the amide intermediate and 30 mL of 2.5 N NaOH was warmed to 70-80 °C for three hours. The clear aqueous solution was cooled and acidified to pH 5 with concentrated HCl. The white precipitate that formed was collected by filtration and washed with H<sub>2</sub>O to afford the desired 1,3-dipropyl-8-[3-(benzoyloxymethyl)-oxazol-5-yl]xanthine, which was recrystallized from CH<sub>3</sub>OH.

[187] MP: 236-238 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.96 (m, 6H), 1.49 (m, 2H), 1.59 (m, 2H), 3.88 (t, 2H), 3.98 (bs, 2H), 5.60 (s, 2H), 7.25 (s, 1H), 7.74

(m, 3H), 8.00 (m, 2H), 14.50 (s, 1H).

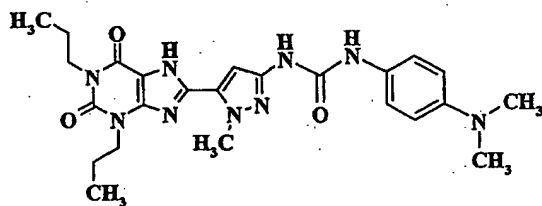
### Example 50 - Preparation of Compound AS20



[188] Using 1,3-dipropyl-5,6-diaminouracil and 3-[3-(benzoyloxymethyl)oxazol-5-yl]acrylic acid, the requisite intermediate was prepared, as described for Example 41. The product was treated with sodium hydride, followed by methyl iodide in THF to provide the desired product.

[189] MP: 165 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.85 (m, 6H), 1.59 (m, 2H), 1.72 (m, 2H), 3.85 (t, 2H), 3.98 (t, 2H), 4.03 (s, 3H), 5.50 (s, 2H), 7.30 (s, 1H), 7.57 (m, 3H), 7.59 (d, 2H, J = 8Hz), 8.03 (d, 2H, J = 8Hz).

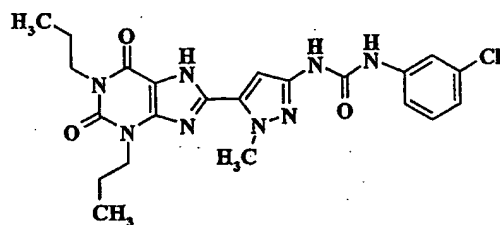
### Example 51 - Preparation of Compound AS53



[190] To a solution of 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (3 mmol, Example 1) in 1,4-dioxane at room temperature was added 4-(dimethylaminophenyl)isocyanate (3.2 mmol). The mixture was stirred overnight at room temperature, quenched by the addition of water, and the precipitated product collected by filtration. Purification was achieved by column chromatography on silica gel.

[191] MP: 266-268 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 2.80 (s, 6H), 3.83 (m, 2H), 3.98 (m, 2H), 4.10 (s, 3H), 6.69 (d, 1H, J = 8.0Hz), 6.94 (d, 1H, J = 8.0Hz), 7.1 (s, 1H), 7.27 (d, 2H, J = 8.0 Hz), 8.64 (s, 1H), 8.98 (s, 1H), 14.0 (s, 1H).

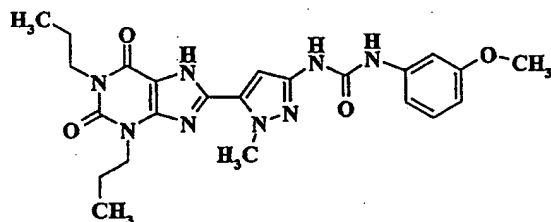
### Example 52 - Preparation of Compound AS54



[192] Using 3-chlorophenylisocyanate and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[193] MP: >300 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 3.83 (m, 2H), 3.98 (m, 2H), 4.10 (s, 3H), 7.01 (m, 1H), 7.19 (s, 1H), 7.30 (m, 2H), 7.70 (s, 1H), 9.03 (s, 1H), 9.15 (s, 1H), 14.0 (s, 1H).

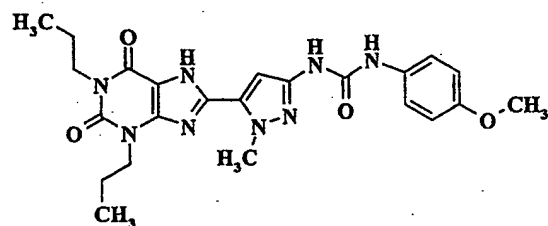
### Example 53 - Preparation of Compound AS55



[194] Using 3-(methoxy)phenylisocyanate and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[195] MP: >300 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 3.82 (s, 3H), 3.86 (m, 2H), 3.98 (m, 2H), 4.10 (s, 3H), 6.54 (d, 1H, J = 8.0Hz), 6.90 (d, 1H, J=8.0Hz), 7.10 (s, 1H), 7.24 (m, 2H), 8.90 (s, 1H), 9.07 (s, 1H), 14.0 (s, 1H).

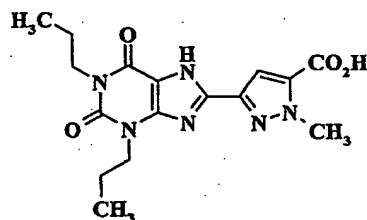
### Example 54 – Preparation of Compound AS49



[196] Using 4-(methoxy)phenylisocyanate and 1,3-dipropyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (Example 1, Compound AS3).

[197] Yield: 98 % MP: >300° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.80 (m, 6H); 1.62 (m, 2H); 1.70 (m, 2H); 3.68 (s, 3H); 3.75 (m, 2H); 4.02 (m, 2H); 4.22 (s, 3H); 7.00 (d, 2H, J = 8.00 Hz); 7.25 (s, 1H); 7.32 (d, 2H, J = 8.00 Hz); 8.82 (s, 1H); 8.95 (s, 1H); 14.01 (s, 1H).

### Example 55 – Preparation of Compound AS1

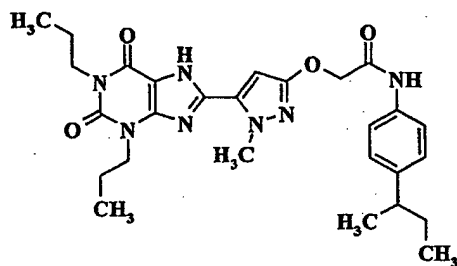


[198] To a solution of 1,3-dipropyl-5,6-diaminouracil (2.2 mmol) in methanol (10 mL) was added an equimolar amount of 1-methyl-1H-pyrazole-3,5-dicarboxylic acid 5-ethyl ester and DCl (2.21 mmol). The reaction mixture was stirred at room temperature for 4-5 h with monitoring by TLC. At completion, the reaction mixture was concentrated in vacuo and water added. The intermediate amide precipitated and was collected by filtration. The solid thus collected was dissolved in methanol (10 mL), 2.5 N NaOH (15 mL) added, and the mixture heated to 70-80° C for 12 hours. After removal of the methanol, the residue was taken up in water, acidified to pH 4-5 with HCl, and the resultant precipitate collected by filtration.

The desired product was purified by flash chromatography on silica gel, eluting with ethyl acetate / petroleum ether.

[199] Yield: 40 %; MP: >300° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.93 (m, 6H); 1.58 (m, 2H); 1.75 (m, 2H); 3.88 (m, 2H); 3.98 (m, 2H); 4.01 (s, 3H); 7.43 (s, 1H); 13.60 (bs, 2H).

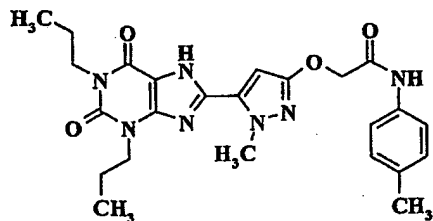
### Example 56 – Preparation of Compound AS91



[200] Using 4-(sec-butyl)aniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[201] Yield: 36 %; MP: 240-242° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.74 (t, 3H, J = 8.00); 0.85 (m, 9H); 1.15 (d, 3H, J = 8.00); 1.51 (m, 2H); 1.55 (m, 2H); 3.86 (m, 2H); 4.00 (m, 2H); 4.06 (s, 3H); 4.74 (s, 2H); 6.50 (s, 1H); 7.12 (d, 2H, J = 8.00); 7.52 (d, 2H, J = 8.00); 10.02 (s, 1H); 13.93 (s, 1H).

### Example 57 – Preparation of Compound AS92



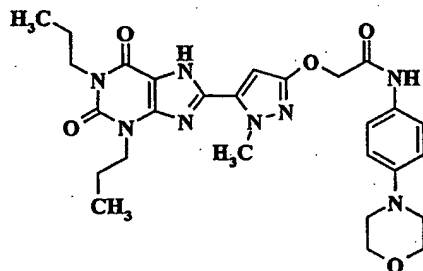
[202] Using 4-(methyl)aniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method

described in Example 36.

**[203]** Yield: 38 %; MP: 256-257° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H); 1.56 (m, 2H); 1.73 (m, 2H); 2.24 (s, 3H); 3.84 (m, 2H); 3.94 (m, 2H); 4.05 (s, 3H); 4.74 (s, 2H); 6.51 (s, 1H); 7.12 (d, 2H, J = 8.10); 7.50 (d, 2H, J = 8.15); 10.01 (s, 1H); 13.94 (s, 1H).

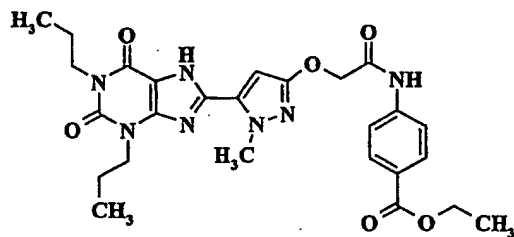
### Example 58 – Preparation of Compound AS93

**[204]** Using 4-(N-morpholino)aniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.



**[205]** Yield: 46 %; MP: 296-298° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H); 1.57 (m, 2H); 1.75 (m, 2H); 3.03 (m, 4H); 3.71 (m, 4H); 3.74 (m, 2H); 3.85 (m, 2H); 4.03 (s, 3H); 4.71 (s, 2H); 6.46 (s, 1H); 6.89 (d, 2H, J = 8.27); 7.48 (d, 2H, J = 8.22); 9.89 (s, 1H); 13.86 (bs, 1H).

### Example 59 – Preparation of Compound AS94



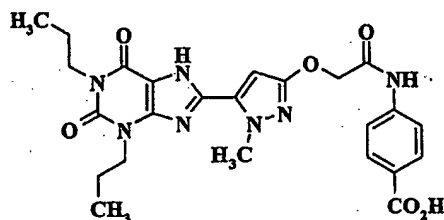
**[206]** Using ethyl 4-(amino)benzoate and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method



described in Example 36.

[207] Yield: 48 %; MP: 294° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H); 1.30 (m, 3H, J = 8.00); 1.58 (m, 2H); 1.62 (m, 2H); 3.85 (m, 2H); 3.96 (m, 2H); 4.03 (s, 3H); 4.24 (q, 2H, J = 8.00); 4.80 (s, 2H); 6.44 (s, 1H); 7.77 (d, 2H, J = 8.00); 7.92 (d, 2H, J = 8.00); 10.46 (s, 1H); 13.92 (s, 1H).

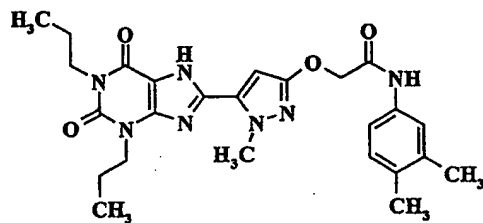
### Example 60 – Preparation of Compound AS95



[208] Using 4-(amino)benzoic acid and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[209] Yield: 38 %; MP: >300° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H); 1.56 (m, 2H); 1.73 (m, 2H); 3.86 (m, 2H); 3.98 (m, 2H); 4.06 (s, 3H); 4.81 (s, 2H); 6.49 (s, 1H); 7.74 (d, 2H, J = 8.70); 7.80 (d, 2H, J = 8.58); 10.44 (s, 1H); 13.92 (s, 1H).

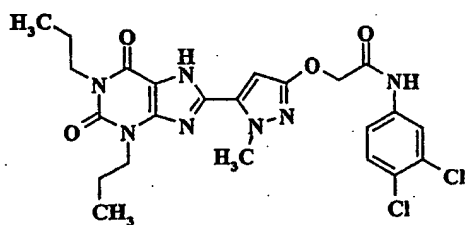
### Example 61 – Preparation of Compound AS99



[210] Using 3,4-dimethylaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[211] Yield: 65 %; MP: 264-265° C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.88 (m, 6H); 1.57 (m, 2H); 1.73 (m, 2H); 2.16 (m, 6H); 3.83 (m, 2H); 3.98 (m, 2H); 4.06 (s, 3H); 4.73 (s, 2H); 6.51 (s, 1H); 7.31 (m, 1H); 7.34 (m, 2H); 9.93 (s, 1H); 13.90 (s, 1H).

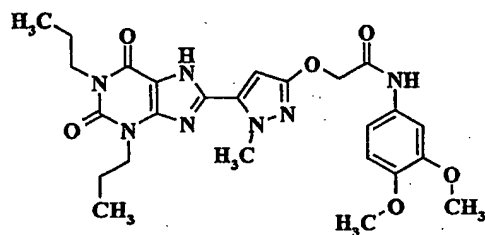
### Example 62 – Preparation of Compound AS100



[212] Using 3,4-dichloroaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[213] Yield: 55 %; MP: 258° C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.88 (m, 6H); 1.57 (m, 2H); 1.72 (m, 2H); 3.84 (m, 2H); 4.00 (m, 2H); 4.06 (s, 3H); 4.78 (s, 2H); 6.52 (s, 1H); 7.57 (s, 2H); 8.02 (s, 1H); 10.42 (s, 1H); 13.94 (s, 1H).

### Example 63 – Preparation of Compound AS101

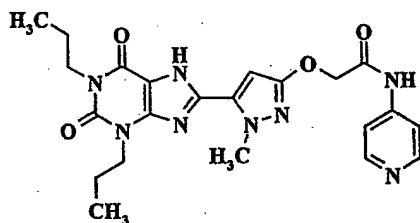


[214] Using 3,4-dimethoxyaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[215] Yield: 60 %; MP: 291-293° C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.88 (m, 6H); 1.59 (m, 2H); 1.77 (m, 2H); 3.71 (m, 6H); 3.87 (m, 2H); 4.00 (m, 2H); 4.07

(s, 3H); 4.73 (s, 2H); 6.51 (s, 1H); 6.89 (m, 1H); 7.14 (m, 1H); 7.33 (m, 1H); 9.95 (s, 1H); 13.97 (s, 1H).

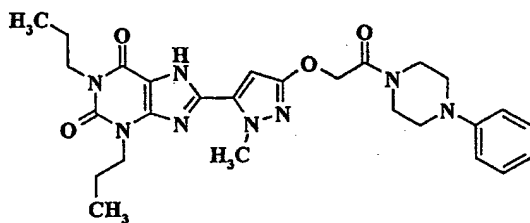
### Example 64 – Preparation of Compound AS89



**[216]** Using 4-aminopyridine and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

**[217]** Yield: 35 %; MP: 248-251° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.9 (m, 6H); 1.55 (m, 2H); 1.67 (m, 2H); 3.89 (m, 2H); 4.00 (m, 2H); 4.05 (s, 3H); 4.82 (s, 2H); 6.44 (s, 1H); 7.64 (d, 2H, J = 8.80); 7.93 (d, 2H, J = 8.92); 10.43 (s, 1H); 13.95 (bs, 1H).

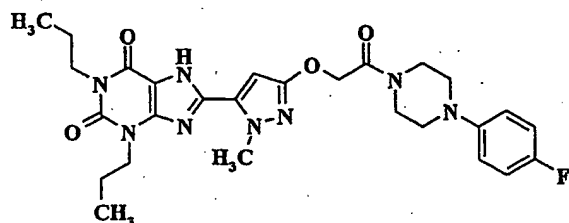
### Example 65 – Preparation of AS70



**[218]** Using N-phenyl-piperazine and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

**[219]** Yield: 38 %; MP: 273-274° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H); 1.69 (m, 2H); 1.71 (m, 2H); 3.18 (m, 4H); 3.57 (m, 4H); 3.86 (m, 2H); 4.00 (m, 2H); 4.05 (s, 3H); 4.93 (s, 2H); 6.46 (s, 1H); 6.81 (m, 1H); 6.96 (d, 2H, J = 8.00); 7.21 (t, 2H, J = 8.00); 13.92 (s, 1H).

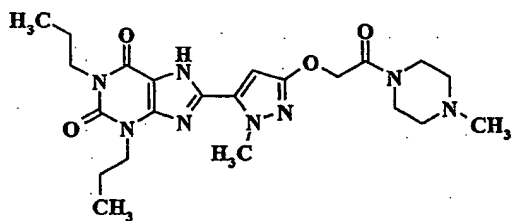
## Example 66 – Preparation of AS72



[220] Using N-(4-fluorophenyl)-piperazine and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[221] Yield: 40 %; MP: 235-237° C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.87 (m, 6H); 1.57 (m, 2H); 1.74 (m, 2H); 3.09 (m, 4H); 3.58 (m, 4H); 3.84 (m, 2H); 3.95 (m, 2H); 4.05 (s, 3H); 4.92 (s, 2H); 6.46 (s, 1H); 7.01 (m, 4H); 13.92 (s, 1H).

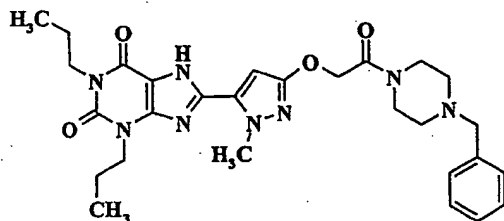
## Example 67 – Preparation of AS87



[222] Using N-methyl-piperazine and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[223] Yield: 56 %; MP: 192-194° C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.87 (m, 6H); 1.06 (m, 2H); 1.20 (m, 2H); 2.39 (m, 4H); 3.39 (m, 4H); 3.75 (m, 2H); 3.90 (s, 3H); 4.12 (m, 2H); 4.04 (s, 3H); 4.85 (s, 2H); 6.92 (s, 1H); 13.92 (s, 1H).

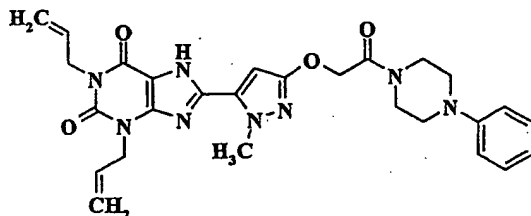
### Example 68 – Preparation of AS90



[224] Using N-benzyl-piperazine and 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 36), according to the method described in Example 36.

[225] Yield: 32 %; MP: 236-237° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H); 1.08 (m, 2H); 1.12 (m, 2H); 2.39 (m, 4H); 3.39 (m, 4H); 3.50 (s, 2H); 3.86 (m, 2H); 4.00 (m, 2H); 4.04 (s, 3H); 4.85 (s, 2H); 6.42 (s, 1H); 7.31 (m, 5H); 13.92 (s, 1H).

### Example 69 – Preparation of AS96



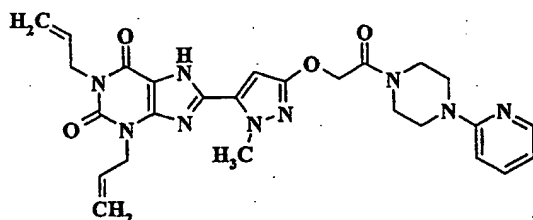
[226] To a solution of ethyl (5-carboxy-1-methylpyrazol-3-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) was added a solution of 1,3-diallyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture was stirred at room temperature for two hours, the solvent was then removed *in vacuo*, water added, and the solid that formed was collected by filtration and washed with additional cold water. The intermediate amide was heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 2-[5-(1,3-diallyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid.

[227] Condensation of 2-[5-(1,3-diallyl-xanthin-8-yl)-1-methyl-pyrazol-3-

yl)oxyacetic acid (0.5 mmol) and N-phenyl-piperazine (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

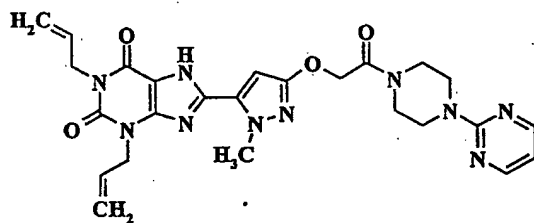
[228] Yield: 27 %; MP: 289-290° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.17 (m, 4H); 3.57 (m, 4H); 4.05 (s, 3H); 4.51 (m, 2H); 4.64 (m, 2H); 4.93 (s, 2H); 5.11 (m, 4H); 5.89 (m, 2H); 6.46 (s, 1H); 6.81 (m, 1H); 6.96 (d, 2H, J = 8.13); 7.23 (t, 2H, J = 8.00); 14.00 (s, 1H).

### Example 70 – Preparation of AS105



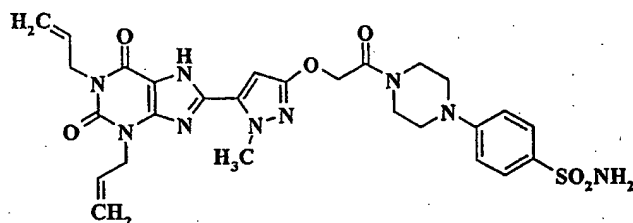
[229] Using N-(pyridin-2-yl)-piperazine and 2-[5-(1,3-diallyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 69), according to the method described in Example 69.

### Example 71 – Preparation of AS106



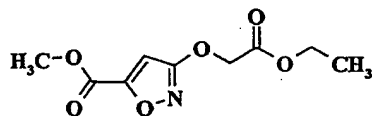
[230] Using N-(pyrimidin-2-yl)-piperazine and 2-[5-(1,3-diallyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 69), according to the method described in Example 69.

### Example 72 – Preparation of AS109



[231] Using N-(4-sulfonamidophenyl)-piperazine and 2-[5-(1,3-diallyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (Example 69), according to the method described in Example 69.

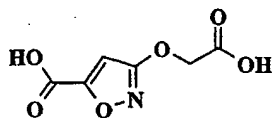
### Example 73 – Preparation of ethyl (5-(methoxycarbonyl)-isoxazol-3-yl)oxyacetate



[232] To a solution of methyl 3-hydroxy-isoxazole-5-carboxylate (7.14 mmol) in acetone (30 mL), was added potassium carbonate (1.2 g, 8.6 mmol) and ethyl bromoacetate (8.6 mmol). The reaction mixture was heated at reflux for 2 h, monitoring by TLC. At completion, acetone was removed in vacuo and the residue partitioned between water and ethyl acetate (50 mL). The organic layer was dried ( $\text{MgSO}_4$ ), filtered, and evaporated to afford the desired intermediate.

[233] Yield: 81%; MP: 66-67° C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (t, 3H,  $J = 7.22$ ); 3.96 (s, 3H); 4.27 (q, 2H,  $J = 7.21$ ); 4.87 (s, 2H); 6.65 (s, 1H).

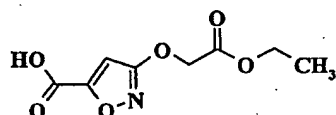
### Example 74 – Preparation of (5-carboxyisoxazol-3-yl)oxyacetic acid



[234] A solution of ethyl (5-(methoxycarbonyl)isoxazol-3-yl)oxyacetate (4 mmol, Example 73) in methanol (60 mL) and 5% aqueous NaOH is heated at reflux for 1 hour. At the end of this time, the methanol is removed, the residue diluted with additional water, and acidified to pH = 4 with hydrochloric acid. The resulting precipitate is collected by filtration, washed with cold water, and dried.

[235] Yield: 90 %; MP: > 300° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 4.71 (s, 2H); 6.22 (s, 1H); 11.30 (bs, 1H); 14.75 (bs, 1H).

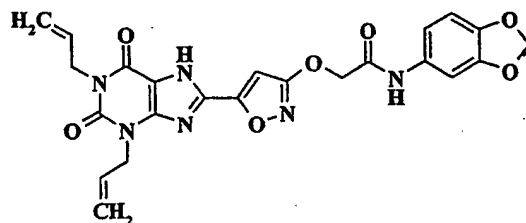
### Example 75 – Preparation of ethyl (5-carboxyisoxazol-3-yl)oxyacetate



[236] (5-Carboxyisoxazol-3-yl)oxyacetic acid (4.0 mmol, Example 74) is dissolved in ethanol (50 mL), to which is added a catalytic amount of p-toluenesulfonic acid (100 mg). After stirring overnight at room temperature, the ethanol was removed and the residue was recrystallized from ethanol/water.

[237] Yield: 70%; MP: 145-150° C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.40 (t, 3H, J = 7.18); 4.20 (q, 2H, J = 7.21); 4.90 (s, 2H); 6.75 (s, 1H); 11.35 (bs, 1H).

### Example 76 – Preparation of AS74



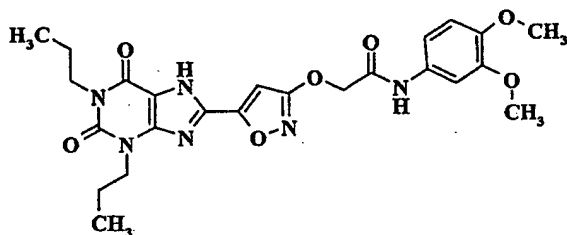
[238] To a solution of ethyl (5-carboxyisoxazol-3-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) was added a solution of 1,3-



dipropyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture was stirred at room temperature for two hours, the solvent was then removed *in vacuo*, water added, and the solid that formed was collected by filtration and washed with additional cold water. The intermediate amide was heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 2-[5-(1,3-dipropyl-xanthin-8-yl)-isoxazol-3-yl]oxyacetic acid.

[239] Condensation of 2-[5-(1,3-dipropyl-xanthin-8-yl)-isoxazol-3-yl]oxyacetic acid (0.5 mmol) and 3,4-methylenedioxyaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

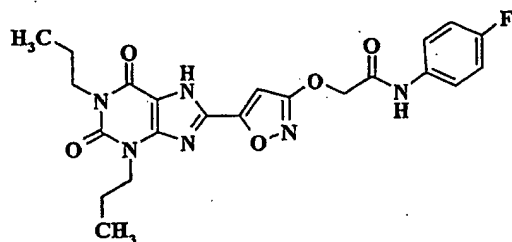
#### Example 77 – Preparation of AS76



[240] Using 3,4-dimethoxyaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-isoxazol-3-yl]oxyacetic acid (Example 76), according to the method described in Example 76.

[241] Yield: 36 %; MP: 253-255° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H); 1.55 (m, 2H); 1.70 (m, 2H); 3.72 (s, 6H); 3.85 (m, 2H); 3.97 (m, 2H); 4.90 (s, 2H); 6.90 (m, 2H); 7.12 (m, 1H); 7.30 (s, 1H); 10.10 (bs, 1H); 14.60 (bs, 1H).

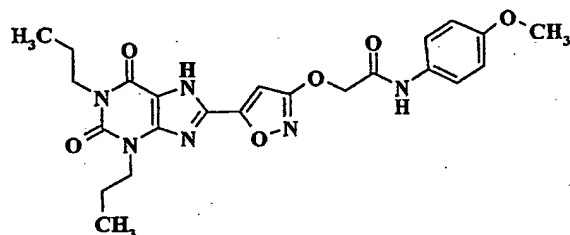
### Example 78 – Preparation of AS73



**[242]** Using 4-fluoroaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-isoxazol-3-yl]oxyacetic acid (Example 76), according to the method described in Example 76.

**[243]** Yield: 28 %; MP: 287° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H); 1.55 (m, 2H); 1.70 (m, 2H); 3.85 (m, 2H); 3.97 (m, 2H); 4.93 (s, 2H); 6.90 (s, 1H); 7.18 (m, 2H); 7.62 (m, 2H); 10.29 (bs, 1H); 14.60 (bs, 1H).

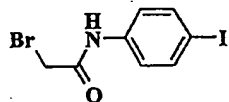
### Example 79 – Preparation of AS75



**[244]** Using 4-methoxyaniline and 2-[5-(1,3-dipropyl-xanthin-8-yl)-isoxazol-3-yl]oxyacetic acid (Example 76), according to the method described in Example 76.

**[245]** Yield: 38 %; MP: 285-287° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H); 1.59 (m, 2H); 1.68 (m, 2H); 3.71 (s, 3H); 3.85 (m, 2H); 3.97 (m, 2H); 4.90 (s, 2H); 6.91 (m, 3H); 7.50 (m, 2H); 10.09 (s, 1H); 14.56 (bs, 1H).

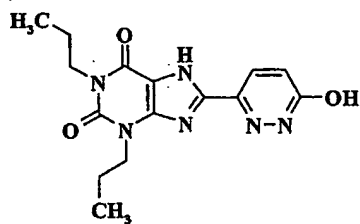
### Example 80 – Preparation of 2-bromo-N-(4-iodophenyl)acetamide



[246] To a solution of 4-iodoaniline (14.5 mmol) in anhydrous dichloromethane at 0° C was added  $\alpha$ -bromo-acetyl bromide (1.4 mL) and triethylamine (15 mmol). The mixture was warmed to room temperature, stirred for 1 h, the solvent removed, and residue dissolved in 5% hydrochloric acid. The aqueous solution was extracted with ethyl acetate, the organic layer washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated. The solid residue was purified by recrystallization from ethyl acetate to afford the desired intermediate.

[247] Yield: 60%; MP: 185° C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4.93 (s, 2H); 8.24 (d, 2H, J = 8.00); 8.58 (d, 2H, J = 8.00); 9.02 (bs, 1H).

### Example 81 – Preparation of 1,3-dipropyl-8-(6-hydroxy-pyridazin-3-yl)-xanthine

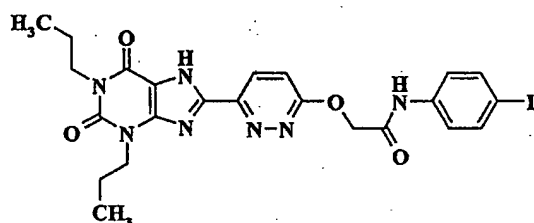


[248] To a solution of 1,3-dipropyl-5,6-diaminouracil (2.2 mmol) in methanol was added an equimolar amount of 6-hydroxy-pyridazine-3-carboxylic acid, followed by a slight excess of DCI ((N-(3-(dimethylamino)propyl)-N'-ethylcarbodiimide hydrochloride). The mixture was stirred at room temperature for 4-5 hours until complete by TLC. Water was then added and the precipitate removed by filtration. The solid was dissolved in 10% aqueous NaOH (20 mL), then heated at 70° C for 30 minutes. After

cooling to room temperature, the reaction mixture was acidified to pH = 5 with 10% hydrochloric acid and the precipitated product collected by filtration.

[249] Yield: 30 %; MP: 216° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.87 (m, 6H); 1.65 (m, 4H); 3.5 (bs, 1H), 3.84 (m, 2H); 3.97 (m, 2H); 6.99 (d, 1H); 8.04 (d, 1H); 13.32 (bs, 1H).

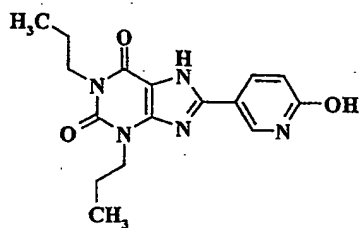
### Example 82 – Preparation of AS85



[250] To a solution of 1,3-dipropyl-8-(6-hydroxy-pyridazin-3-yl)-xanthine (0.20 mmol, Example 81) in anhydrous dimethylformamide (10 mL) was added an equimolar amount of triethylamine. The reaction mixture was stirred at room temperature for 10 minutes, followed by the addition of 2-bromo-N-(4-iodophenyl)acetamide (0.20 mmol, Example 80). After stirring at room temperature overnight, the solvent was distilled off, the residue was taken up in cold water, and the precipitated product collected by filtration. The product was further purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol.

[251] Yield: 28 %; MP: 310° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.86 (m, 6H); 1.55 (m, 2H); 1.76 (m, 2H); 3.80 (m, 2H); 4.03 (m, 2H); 5.58 (s, 2H); 7.04 (d, 1H, J = 9.92); 7.37 (d, 2H, J = 8.64); 7.65 (d, 2H, J = 8.55); 8.09 (d, 1H, J = 10.01); 10.45 (s, 1H); 13.30 (bs, 1H).

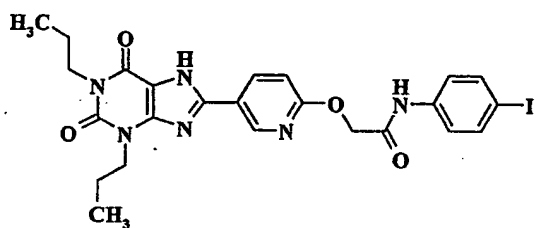
## Example 83 – Preparation of AS103



[252] To a solution of 1,3-dipropyl-5,6-diaminouracil (2.2 mmol) in methanol was added an equimolar amount of 2-hydroxy-pyridine-5-carboxylic acid, followed by a slight excess of DCI ((N-(3-(dimethylamino)propyl)-N'ethylcarbodiimide hydrochloride). The mixture was stirred at room temperature for 4-5 hours until complete by TLC. Water was then added and the precipitate removed by filtration. The solid was dissolved in 10% aqueous NaOH (20 mL), then heated at 70° C for 30 minutes. After cooling to room temperature, the reaction mixture was acidified to pH = 5 with 10% hydrochloric acid and the precipitated product collected by filtration.

[253] Yield: 25 %; MP: >300° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.88 (m, 6H); 1.60 (m, 4H); 3.84 (bs, 1H); 3.84 (m, 2H); 3.97 (m, 2H); 6.47 (d, 1H); 8.08 (m, 1H); 8.20 (m, 1H); 13.30 (bs, 1H).

## Example 84 – Preparation of AS81

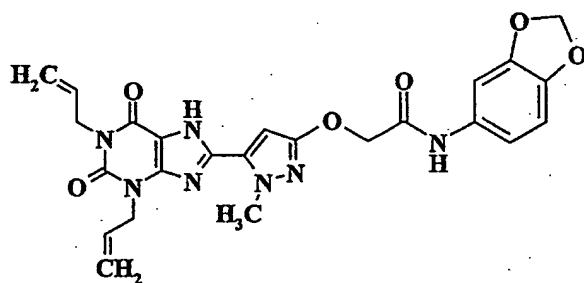


[254] To a solution of 1,3-dipropyl-8-(2-hydroxy-pyridin-5-yl)-xanthine (0.20 mmol, Example 81) in anhydrous dimethylformamide (10 mL) was added an equimolar amount of triethylamine. The reaction mixture was stirred at

room temperature for 10 minutes, followed by the addition of 2-bromo-N-(4-iodophenyl)acetamide (0.20 mmol, Example 80). After stirring at room temperature overnight, the solvent was distilled off, the residue was taken up in cold water, and the precipitated product collected by filtration. The product was further purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol.

[255] Yield: 25 %; MP: 293° C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.86 (m, 6H); 1.55 (m, 2H); 1.76 (m, 2H); 3.80 (m, 2H); 3.89 (m, 2H); 5.21 (s, 2H); 6.37 (d, 1H,  $J$  = 9.46); 7.45 (d,

### Example 85 - Preparation of Compound AS68a



[256] To a solution of ethyl (5-carboxy-1-methylpyrazol-3-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) was added a solution of 1,3-diallyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture was stirred at room temperature for two hours, the solvent was then removed *in vacuo*, water added, and the solid that formed was collected by filtration and washed with additional cold water. The intermediate amide was heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid.

[257] Condensation of 2-[5-(1,3-dipropyl-xanthin-8-yl)-1-methyl-pyrazol-3-yl]oxyacetic acid (0.5 mmol) and 3,4-methylenedioxyaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide afforded the desired product.

[258] MP: 288-289 °C;  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  2.50 (s, 3H), 4.51 (d, 2H), 4.62 (d, 2H), 4.72 (s, 2H), 5.07 (d, 1H), 5.10 (d, 1H), 5.15 (s, 1H), 5.18 (d, 1H), 5.90 (m, 2H), 5.98 (s, 2H), 6.51 (s, 1H), 6.87 (d, 1H,  $J = 8.44\text{Hz}$ ), 7.01 (d, 1H), 7.32 (s, 1H), 10.01 (s, 1H); 14.01 (bs, 1H).

## Preparation of Radioligand Compounds

[259] The compounds can be labeled with any suitable radiolabel. Examples of suitable radiolabels include tritium ( $^3\text{H}$ ) and carbon radioisotopes (e.g.  $^{14}\text{C}$ ), but any substantially non-toxic radiolabel commonly used in pharmacokinetic studies can be used. Means for incorporating radiolabels onto organic compounds are well known to those of skill in the art.

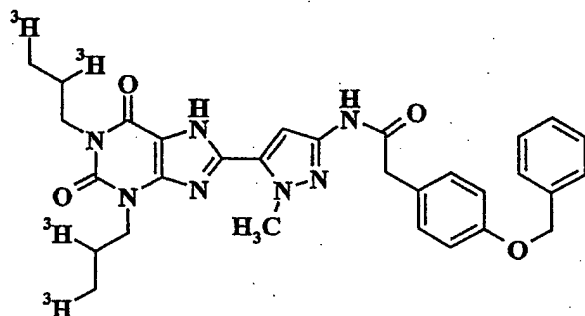
[260] When the compounds are synthesized from a starting 1,3-dialkyl-5,6-diaminouracil, incorporation of a radiolabel is fairly straightforward. For example, the diaminouracil can be obtained containing a suitable radiolabel. As an alternate, the diaminouracil can be obtained with one or more sites of unsaturation in an attached substituent (e.g. iso-propylene in place of iso-propyl). The unsaturated double bond can then be reacted with tritium in the presence a suitable catalyst, for example, palladium on charcoal or other known hydrogenation catalysts. Using the radiolabeled diaminouracil and following the methods of synthesis herein described will result in the corresponding radiolabeled compound.

[261] It has been established by the inventors, as well as known by those skilled in the art, that  $^3\text{H}$  and  $^{14}\text{C}$  labeled compounds have binding affinity to the adenosine  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and  $A_3$  receptor subtypes comparable to that of corresponding non-labeled forms.

[262] In another embodiment, the radiolabel can be incorporated into the molecule while the ring system is being put together. As discussed above with respect to the synthesis of the compounds of Formula II, various tricyclic compounds of Formula VI are hydrolyzed with HCl to give

triazoles of Formula VII, which are cyclized to with cyanamide at reflux in the presence of para-toluenesulfonic acid, as shown in Scheme I. It is relatively straightforward to incorporate a  $^{14}\text{C}$  label at this step in the synthesis using  $^{14}\text{C}$  labeled cyanamide.

### Example 86 - Preparation of Radioligand of Compound AS16



[263] A solution of 1,3-diallyl-5,6-diaminouracil (0.7 g, 0.003 mol), 1-methyl-3-(benzyloxycarbonylamino)-pyrazole-5-carboxylic acid (0.8 g, 0.003 mol), and EDCI (0.6 g, 0.003 mol) in 50 mL of  $\text{CH}_3\text{OH}$  is stirred at room temperature for two hours. Excess  $\text{CH}_3\text{OH}$  is evaporated *in vacuo* to give a yellow solid that is collected by filtration and washed with  $\text{H}_2\text{O}$  to give the amide intermediate.

[264] A mixture of the amide intermediate and 30 mL of 2.5 N NaOH is warmed to 70-80 °C for three hours. The clear aqueous solution is cooled and acidified to pH 5 with concentrated HCl. The white precipitate that forms is collected by filtration and washed with  $\text{H}_2\text{O}$  to afford the desired 1,3-diallyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine, which is recrystallized from  $\text{CH}_3\text{OH}$ . A solution of 4-(benzyloxy)phenylacetic acid (0.196 mmol) in 3 mL of thionyl chloride is stirred at 70 °C for four hours, then excess thionyl chloride removed in a nitrogen stream.

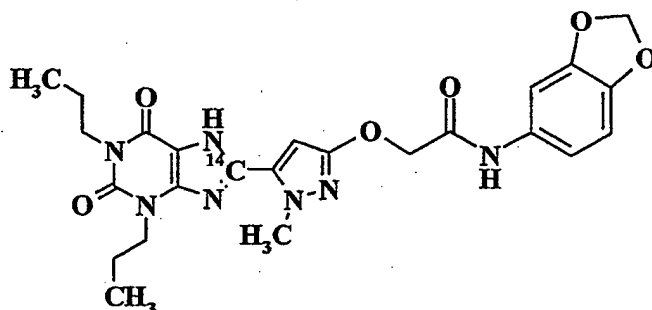
[265] A solution of 1,3-diallyl-8-(3-amino-1-methylpyrazol-5-yl)xanthine (0.151 mmol, Example 1) and 0.04 mL of anhydrous triethylamine in 10 mL of  $\text{CH}_2\text{Cl}_2$ :  $\text{CH}_3\text{OH}$  (1:1) is added and the mixture is stirred at room



temperature for 24 hours, monitoring by TLC. At completion, the solvent is evaporated, the residue is dissolved in ethyl acetate, and the solution washed with saturated aqueous  $\text{NaHCO}_3$  and brine. The organic layer is dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated *in vacuo*. The desired intermediate is purified by column chromatography on silica gel.

- [266]** To a suspension of 10% Pd/C (5 mg) in  $\text{CH}_3\text{CH}_2\text{OH}$  (10 mL) is added a solution of 1,3-diallyl-8-(3-(2-(4-(benzyloxy)phenyl)acetylamino)-1-methylpyrazol-5-yl)xanthine in  $\text{CH}_3\text{CH}_2\text{OH}$  (3 mL). The mixture is evacuated and charged with tritium gas to 50 psi, then shaken at room temperature for 16 hours. The mixture is evacuated, the solution filtered to remove catalyst, and the solution evaporated *in vacuo*. The residue is purified by column chromatography to provide the desired tritiated analogue, identical chromatographically to Example 7.

### Example 87 - Preparation of Radioligand of Compound AS68



- [267]** To a solution of ethyl (5- $^{14}\text{C}$ -carboxy-1-methylpyrazol-3-yl)oxyacetic acid (0.5 mmol) and EDCI (0.5 mmol) in methanol (20 mL) is added a solution of 1,3-dipropyl-5,6-diaminouracil (0.5 mmol), dissolved in methanol (20 mL). The mixture is stirred at room temperature for two hours, the solvent is then removed *in vacuo*, water is added, and the solid that forms is collected by filtration and washed with additional cold water. The intermediate amide is heated in 20 mL of 2.5 N NaOH at 70 °C for 30 minutes to afford the desired 2-[5-(1,3-dipropyl-8- $^{14}\text{C}$ -xanthin-8-yl)-1-

methyl-pyrazol-3-yl)oxyacetic acid.

- [268] Condensation of 2-[5-(1,3-dipropyl-[ $^{14}\text{C}$ ]-8-[xanthin-8-yl])-1-methyl-pyrazol-3-yl]oxyacetic acid (0.5 mmol) and 3,4-methylenedioxyaniline (1.3 mmol) in the presence of EDCI (1.12 mmol) and HOBt (1.14 mmol) in anhydrous dimethylformamide affords the desired [ $^{14}\text{C}$ ]-labeled product, identical chromatographically with Example 39.

## Preparation of Fluorescently Labeled Compounds

- [269] As with the radiolabeled compounds, the synthesis of fluorescently labeled compounds is relatively straightforward. Chemical bonding of fluorescent labels, with or without a linking or tethering group, to oligomeric compounds, is well known in the art (see for example: Hill, J. J. and Royer, C. A., *Methods Enzymol.*, 1997, 278, 390-416; and Amann *et al.*, *Microbiol. Rev.*, 1997, 20, 191-200). Typically, the fluorescent label is attached via a covalent bond using a tethering moiety. Additional techniques and uses of fluorescently labeled compounds are disclosed in U.S. Patent 6,127,124 to Leeds *et al.*, incorporated herein by reference.

## Utility

- [270] The compounds of the present invention can be used *in vitro* for scientific studies requiring highly selective  $\text{A}_{2\text{B}}$  radioligands. For example, the present inventive 8-heteroaryl xanthine derivatives may be used to probe adenosine receptors in order to isolate or characterize the receptors.
- [271] Additionally, the compounds of the present invention can be used *in vivo* for treating diseases induced by activation of the adenosine  $\text{A}_{2\text{B}}$  receptor and inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent

diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; and apnea of preterm infants.

**[272]** Furthermore, following the teachings of Belardinelli, the compounds of the present invention may be used for inhibiting cell proliferation in cells that express the A<sub>2B</sub> adenosine receptor including human retinal endothelial cells (HREC). Such uses include treatment for chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; and apnea of preterm infants; myocardial reperfusion injury, inflammatory bowel disease, and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis (MS) and lupus erythematosus.

**[273]** Similarly, the compounds can be used in a method for the treatment of diseases involving microvascular abnormalities of the retina that are mediated by adenosine A<sub>2B</sub> receptors. Such diseases include, but are not limited to, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

**[274]** The compounds of the present invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *i.e.*, orally or parenterally, by intravenous, intramuscular, topical, inhalation or subcutaneous routes. Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets or may be incorporated

directly with the food of the patient's diet.

- [275] For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1 % of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.
- [276] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol.
- [277] Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor.
- [278] It is desirable that any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained release preparations and devices.
- [279] The active compound may also be administered intravenously or

intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

**[280]** The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active compound of the present invention that is further adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form is preferably sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium such as, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants.

**[281]** The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and celatin.

**[282]** Sterile injectable solutions are prepared by incorporating the active compound in the required amount of the appropriate solvent with various other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile

injectable solutions, the preferred methods of preparation are vacuum drying and freeze drying techniques, which yield a powder of the active compound plus any additional desired ingredient.

**[283]** For topical administration, the present compounds may be applied in pure form, *i.e.*, when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

**[284]** Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings or sprayed onto the affected area using pump-type or aerosol sprayers.

**[285]** Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

**[286]** Examples of useful dermatological compositions which, can be used to deliver the compounds of present invention to the skin are known in the art, for example, as described in U.S. Patent numbers 4,608,392, 4,992,478, 4,559,157 and 4,820,508.

**[287]** Useful dosages of the compounds of the present invention can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the: extrapolation of effective dosages in

mice, and other animals, to humans are known to the art; for example, see U.S. Patent number 4,938,949.

- [288] Generally, the concentration of the compound(s) of the present invention in a liquid composition, such as a lotion, will be from about 0.01-25 wt-%, preferably from about 0.1-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt%.
- [289] The amount of the compound or an active salt or derivative required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the administering physician or clinician. In general, a suitable dose will be in the range of from about 0.001 mg/kg/day to about 20 mg/kg/day. For example, a dosage may be from 0.002 mg/kg/day to about 10 mg/kg of body weight per day, preferably in the range of 0.01 mg/kg/day to 1 mg/kg/day, and most preferably in the range of 0.1 mg/kg/day to 5 mg/kg/day.
- [290] The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 µg, conveniently 10 to 750 µg, most conveniently, 50 to 500 µg of active ingredient per unit dosage form.
- [291] The compounds of the invention can be administered by inhalation from an inhaler, insufflator, atomizer or pressurized pack or other means of delivering an aerosol spray. Pressurized packs may use a suitable propellant such as carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The inhalers, insufflators, and atomizers are fully described in pharmaceutical reference books such as Remington's Pharmaceutical Sciences 18th edition (1990) Mack Publishing Co., Easton, PA.
- [292] The desired dose may conveniently be presented in a single dose or as

divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye. Dosages above or below the range cited above are within the scope of the present invention and may be administered to the individual patient if desired and necessary.

- [293] When used in the treatment of treatment for ischemic injury to retinal vessels the compounds of the present invention are preferably formulated in eyedrops suitable for topical application.

### Biological assays

- [294] All synthesized compounds have been tested for their affinity to human  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$  adenosine receptors expressed in Chinese Hamster Ovary cells (CHO) ( $A_1$ ,  $A_{2A}$  and  $A_3$ ) and HEK 293 cells ( $A_{2B}$ ) using cell binding assay techniques known in the art.

- [295] The cells were grown adherently and maintained in Dulbecco's modified Eagle's medium with nutrient mixture F12 without nucleosides at 37°C in 5% CO<sub>2</sub> / 95% air. The cells were washed with phosphate-buffered saline and scraped off flasks in ice cold hypotonic buffer (5 mM Tris HCl, 2 mM EDTA, pH 7.4). The cell suspension was homogenized with a Polytron and the homogenate was centrifuged for 30 minutes at 48,000 g. The resultant membrane pellet was re-suspended in 50 mM Tris HCl buffer at pH 7.4 for  $A_1$  adenosine receptors; in 50 mM Tris HCl 10 mM MgCl<sub>2</sub>, at pH 7.4 for  $A_{2A}$  adenosine receptors; in 50 mM Tris HCl, 10 mM MgCl<sub>2</sub>, 1 mM EDTA, at pH 7.4 for  $A_3$  adenosine receptors and were utilized for binding assays.

- [296] HEK 293 cells transfected with the human recombinant  $A_{2B}$  adenosine receptor were obtained from Receptor Biology, Inc. (Beltsville, MD. USA).

- [297] Binding of [<sup>3</sup>H]-DPCPX to CHO cells transfected with the human



recombinant A<sub>1</sub> adenosine receptor was performed according to the method previously described by Klotz *et al.* 1985. Displacement experiments were performed for 120 minutes at 25°C in 200 µl of buffer containing 1 nM [<sup>3</sup>H]-DPCPX 20 µl of diluted membranes (50 µg of protein/assay) and at least 6 to 8 different concentrations of examined compounds. Non-specific binding was determined in the presence of 10 µM of CHA and this is always less than 10% of the total binding.

**[298]** Binding of [<sup>3</sup>H]ZM-241385 to CHO cells transfected with the human recombinant A<sub>2A</sub> adenosine receptors (50 µg of protein/assay) was performed according to Varani *et al.*, 2000. In competition studies, at least 6-8 different concentrations of compounds were used and non-specific binding was determined in the presence of 1 µM ZM-241385 with an incubation time of 60 minutes at 25°C.

**[299]** Binding of 1 [<sup>3</sup>H]-DPCPX to HEK 293 cells transfected with the human recombinant A<sub>2B</sub> adenosine receptors was performed according to the method described by Varani *et al.*, 2000. In particular, assays were carried out for 60 minutes at 25°C in 100 µl of 50 nM Tris HCl buffer, 10 nM MgCl<sub>2</sub>, 1 mM EDTA, 0.1 mM benzamidine pH 7.4, 2 IU/ml adenosine deaminase containing 40 nM [<sup>3</sup>H]-DPCPX, diluted membranes (20 µg of protein/assay) and at least 6-8 different concentration of tested compounds. Non-specific binding was determined in the presence of 100 µM of NECA and was always less than 30 % of the total binding.

**[300]** Binding of [<sup>3</sup>H]-MRE3008-F20 to CHO cells transfected with the human recombinant A<sub>3</sub> adenosine receptors was performed according to Varani *et al.*, 2000. Competition experiments were carried out in duplicate in a final volume of 250 µl in test tubes containing 1 nM [<sup>3</sup>H]-MRE3008-F20, 50 mM Tris HCl buffer, 10 nM MgCl<sub>2</sub>, pH 7.4 and 100 µl of diluted membranes (50 µg of protein/assay) and at least 6-8 different concentrations of examined ligands for 120 minutes at 4°C. Non-specific binding was defined as binding in the presence of 1 µM [<sup>3</sup>H]-MRE3008-

F20 and was about 25% of total binding.

- [301] Bound and free radioactivity portions were separated by filtering the assay mixture through Whatman GF/B glass-fiber filters using a Micro-Mate 196 cell harvester (Packard Instrument Company). The filter bound radioactivity was counted on Top Count (efficiency 57%) with Micro-Scint 20. The protein concentration was determined according to a Bio-Rad method (Bradford, 1976) with bovine albumin as reference standard.
- [302] Measurement of cyclic AMP (cAMP) levels in CHO cells transfected with human  $A_{2B}$  adenosine receptors was performed in the following manner. CHO cells transfected with human  $A_{2B}$  adenosine receptors were washed with phosphate-buffered saline, diluted trypsin and centrifuged for 10 minutes at 200 g. The pellet containing the CHO cells ( $1 \times 10^6$  cells/assay) was suspended in 0.5 ml of incubation mixture (mM): 15 mM NaCl, 0.27 mM KCl, 0.037 mM  $\text{NaH}_2\text{PO}_4$ , 0.1 mM  $\text{MgSO}_4$ , 0.1  $\text{CaCl}_2$ , 0.01 mM Hepes, 1 mM MgCl, 0.5 mM glucose, pH 7.4 at 37°C, 2 IU/ml adenosine deaminase and 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (Ro 20-1724) as phosphodiesterase inhibitor and preincubated for 10 minutes in a shaking bath at 37°C.
- [303] The potencies of antagonists studied were determined by antagonism of NECA (100 nM)-induced stimulation of cAMP levels. The reaction was terminated by the addition of cold 6% trichloroacetic acid (TCA). The TCA suspension was centrifuged at 2000 g for 10 minutes at 4°C and the supernatant was extracted four times with water saturated diethyl ether. The final aqueous solution was tested for cAMP levels by a competition protein binding assay. Samples of cAMP standard (0-10 pmoles) were added to each test tube containing the incubation buffer (Tris base 0.1 M, aminophylline 8.0 mM, 2-mercaptoethanol 6.0 mM, pH 7.4) and [ $\text{H}^3$ ]-cAMP in a total volume of 0.5 ml. The binding protein previously prepared from beef adrenals, was added to the samples previously incubated at 4°C for 150 minutes, and after the addition of charcoal were centrifuged at

2000 g for 10 minutes. The clear supernatant was counted in a Beckman scintillation counter.

## Data Analysis

[304] The filter bound radioactivity was counted on a Top Count brand Microplate Scintillation Counter (efficiency 57%) with Micro-Scint 20. The protein concentration was determined according to a Bio-Rad method (Bradford, 1976) with bovine albumin as a standard reference. Inhibitory binding constant,  $K_i$  values were calculated from those of  $IC_{50}$  according to the Cheng and Prusoff equation (Cheng and Prusoff, 1973):

[305] 
$$K_i = IC_{50} / (1 + [C^*]/K_D^*),$$

[306] where  $[C^*]$  is the concentration of the radioligand and  $K_D^*$  is its dissociation constant. The weighted non-linear least-squares curve fitting program LIGAND (Munson & Rodboard, 1980) was used for computer analysis of saturation and inhibition experiments. All data ( $K_i$  and  $IC_{50}$ ) are expressed as geometric means with 95% confidence intervals.

## Results and Discussion

[307] Binding results, expressed as  $K_i$  for the synthesized compounds AS3 to AS69 are reported in Table 1. A binding of greater than 10,000 nM (10  $\mu$ M) is indicated when no appreciable binding was measured. As is seen in Table 1, the compounds of the present invention present a wide range of binding affinities hence making selection of antagonism for various adenosine receptor subtypes possible. For example, a compound such as AS68 is a highly potent  $A_{2B}$  antagonist and retains significant  $A_1$  antagonism. Compound such as AS28 provide less  $A_{2B}$  affinity but are totally selective with no appreciable binding to the other adenosine receptor subtypes.

Table 1 - Binding Affinities to Adenosine Receptors

Compound Number	Ki (nM)			
	<sup>13</sup> HIDPCPX binding to human A1 receptors expressed in CHO cells	[ <sup>3</sup> H]ZM241385 binding to human A2A receptors expressed in CHO cells	[ <sup>3</sup> H]DPCPX binding to human AM receptors expressed in HEK293 cells	[ <sup>3</sup> H]MRE3008F20 binding to human A3 receptors expressed in CHO cells
AS3	201 (172-236)	>1000	235(209-264)	>1000
AS11	900 (811-996)	>1000	35(27-45)	>1000
AS12	>1000	>1000	>1000	>1000
AS13	>1000	>1000	96(80-114)	>1000
AS14	>1000	>1000	>1000	>1000
AS15	>1000	>1000	78(63-96)	>1000
AS16	>1000	>1000	56(42-77)	>1000
AS17	>1000	>1000	103 (79-136)	>1000
AS18	>1000	>1000	>1000	>1000
AS19	>1000	>1000	>1000	>1000
AS21	>1000	>1000	>1000	>1000
AS22	200 (166-240)	>1000	88(84-92)	>1000
AS23	850 (762-946)	>1000	100 (83-120)	>1000
AS24	4481 (3650-5501)	>1000	160(142-179)	>1000
AS25	3227 (2799-3720)	>1000	50(41-60)	>1000
AS26	>1000	>1000	1628 (1374-1930)	>1000
AS27	520 (484-558)	>1000	28(23-33)	>1000
AS28	>1000	>1000	38(33-43)	>1000
AS29	56(47-67)	>1000	13(11-16)	>1000

AS30	100 (83-120)	>1000	90(73-110)	>1000
AS31	163 (137-193)	>1000	111(100-124)	>1000
AS32	746 (659-843)	>1000	190 (172-209)	>1000
AS43	1898(1723-2091)	>1000	130(113-150)	>1000
AS44	>1000	>1000	>1000	>1000
AS56	1793(1460-2201)	2433 (1675-3533)	100(83-120)	>1000
AS57	566(516-621)	1249(856-1822)	18(12-27)	>1000
AS58	>1000	1755 (1343-2292)	342(274-426)	>1000
AS8	>1000	>1000	>1000	>1000
AS9	>1000	>1000	>1000	>1000
AS10	548 (464-648)	>1000	2065 (1866-2284)	>1000
AS38	>1000	>1000	175 (134-229)	>1000
AS40	>1000	>1000	569 (506-640)	>1000
AS7	122 (84-177)	>1000	342(274-426)	>1000
AS36	>1000	>1000	>1000	>1000
AS33	>1000	>1000	>1000	>1000
AS59	>1000	>1000	1012 (819-1250)	>1000
AS64	65(48-86)	>1000	12(7-21)	>1000
AS65	150(132-170)	>1000	20(16-25)	>1000
AS68	200 (180-226)	>1000	5.5 (4.6-6.5)	>1000
AS69	>1000	>1000	86(77-96)	>1000
AS66	467 (400-546)	>1000	303 (260-352)	>1000
AS67	2427(2067-2850)	>1000	132(98-178)	>1000

AS37	140(123-159)	>1000	58(45-74)	>1000
AS35	55(46-65)	>1000	34(26-46)	>1000
AS60	168 (140-201)	>1000	93(82-105)	>1000
AS61	181(127-258)	>1000	185(163-210)	>1000
AS62	72(45-114)	>1000	207 (162-265)	>1000
AS63	49(34-72)	>1000	66(38-116)	>1000
AS4	>1000	>1000	>1000	>1000
AS20	>1000	>1000	>1000	>1000
AS53	2410(1760-3301)	>1000	59(44-81)	>1000
AS54	448 (365-550)	>1000	39 (33-46)	>1000
AS55	1993 (1658-2397)	>1000	90(73-110)	>1000
AS1	>1000	>1000	>1000	>1000
AS49	1440(1250-2211)	>1000	81(70-110)	>1000
AS91	1005(916-1103)	>1000	74(67-81)	>1000
AS92	79(72-86)	>1000	19(12-29)	>1000
AS93	>1000	>1000	86(78-93)	>1000
AS95	>1000	>1000	36(27-47)	>1000
AS99	700(650-760)	>1000	10(8-13)	>1000
AS100	300(240-380)	>1000	16(12-20)	>1000
AS101	>1000	>1000	12(8-17)	>1000
AS89	955(896-1017)	>1000	41(35-48)	>1000
AS70	250(181-348)	>1000	15(10-21)	>1000
AS72	>1000	>1000	55(46-65)	>1000

AS87	>1000	>1000	122(108-136)	>1000
AS90	810(763-859)	>1000	85(66-95)	>1000
AS96	>1000	>1000	24(18-32)	>1000
AS74	>1000	>1000	47(43-52)	>1000
AS76	>1000	>1000	51(44-58)	>1000
AS73	>1000	>1000	70(61-80)	>1000
AS75	>1000	>1000	53(40-69)	>1000
AS81	>1000	>1000	108(75-155)	>1000
AS85	>1000	>1000	>1000	>1000
AS94	>1000	>1000	32(22-45)	>1000
AS103	81	606	4.9	116

**[308]** The compound AS68 has the highest measured affinity for the human  $A_{2B}$  receptors ( $K_i = 5.5$  nM), binding to adenosine  $A_1$  receptors ( $K_i = 200$  nM) but appears to show little or no affinity to human  $A_{2A}$  and  $A_3$  adenosine receptors subtypes. The compounds AS29, AS39, AS57, AS64 and AS65 have good affinity for the human  $A_{2B}$  receptors with an affinity value in the nanomolar range ( $K_i = 9-20$  nM). Other compounds such as AS11, AS27, AS28, AS35 and AS54 showed a  $K_i$  value in the nanomolar range ( $K_i = 28-39$  nM) for  $A_{2B}$  receptors. Compounds AS13, AS15, AS16 and AS17 show affinity in nanomolar range ( $K_i = 56-103$  nM) to the human  $A_{2B}$  receptor, with no appreciable affinity for the other adenosine receptor subtypes.

**[309]** For use as a pharmaceutical preparation, compound AS68 is particularly preferred due to its excellent affinity towards the  $A_{2B}$  receptor ( $K_i = 5.5$  nM) despite some significant  $A_1$  adenosine receptor binding ( $K_i =$

200 nM). Due to strong cardiovascular effects compounds with significant  $A_{2A}$  binding are less preferred.

**[310]** For use as a radioligand and where near total  $A_{2B}$  receptor selectivity is desired compounds such as AS13, AS15, AS16, AS17, AS28 and AS69 are preferred. All have relatively strong  $A_{2B}$  receptor binding ( $K_i$  = 38-103 nM) but without significant binding for any of the other receptor subtypes.

**[311]** Figures 1 through 4 show typical competition curves of compounds AS29, AS57, AS64 and AS68 at  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$  adenosine receptors.

**[312]** Finally, to evaluate the regulation of adenylyl cyclase activity and to test whether the binding parameters correlated with the functional response, the  $IC_{50}$  values were obtained for inhibition of cAMP production by antagonists. In particular, we evaluated the capability of the several compounds to inhibit NECA (100 nM)-stimulated cyclic AMP accumulation.

**[313]** Table 2 summarizes the  $K_i$  values obtained in [ $^3H$ ]-DPCPX binding to  $A_{2B}$  adenosine receptors and the  $IC_{50}$  values for the inhibition of cAMP levels. Of the selected compounds, the most potent adenosine  $A_{2B}$  receptor antagonists were AS64 and AS68 ( $IC_{50}$  = 38 and 88 nM, respectively). Compounds AS29 and AS57 show an  $IC_{50}$  value of  $IC_{50}$  = 93 and 95 nM, respectively. (see also Figure 7). Other tested compounds show an  $IC_{50}$  value in the lower nanomolar range ( $IC_{50}$ =100-152 nM, respectively).

**Table 2 – Comparison of [ $^3H$ ]-DPCPX Binding to cAMP Levels**

	<b>[<math>^3H</math>]-DPCPX binding to human <math>A_{2B}</math> receptors in HEK 293 cells <math>K_i</math> (nM)</b>	<b>Cyclic AMP assay- human <math>A_{2B}</math> receptors in CHO cells <math>IC_{50}</math> (nM)</b>
<b>AS 11</b>	35 (27-45)	103 (92-115)



AS 27	28 (23-33)	128 (114-144)
AS 28	38 (33-43)	120 (103-140)
AS 29	13 (11-16)	93 (84-102)
AS 35	34 (26-46)	152 (136-170)
AS 54	39 (33-46)	136 (115-161)
AS 57	18 (12-27)	95 (90-101)
AS 64	12 (7-21)	88 (82-95)
AS 65	20 (16-25)	108 (91-129)
AS 68	5.5 (4.6-6.5)	38 (29-51)

[314] Each value of Table 2 is the geometric mean (with 95% confidence limits in parentheses) of at least three separate experiments performed in duplicate.

[315] The Spearman's rank correlation coefficient between affinity values of [<sup>3</sup>H]-DPCPX binding to A<sub>2B</sub> adenosine receptor by selected compounds and the IC<sub>50</sub> values in the cAMP assay was 0.89 (P<0.01). A comparison of the K<sub>i</sub> and IC<sub>50</sub> values indicated that high correlation exists between data obtained from binding and cAMP assays (Figure 5).

## Formulations

[316] Formulations of the present invention for medical use comprise an active compound, i.e., a compound of formula (IA) or (IB) together with an acceptable carrier thereof and optionally other therapeutically active ingredients. The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[317] The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of formula (IA) or (IB) together with a

pharmaceutically acceptable carrier thereof.

**[318]** The formulations include, but are not limited to, those suitable for oral, rectal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred are those suitable for oral, parenteral or topical administration.

**[319]** The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier that constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier and then, if necessary, shaping the product into desired unit dosage form.

**[320]** Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or solution in an aqueous liquid or non-aqueous liquid, e.g., a syrup, an elixir, an emulsion or a draught.

**[321]** A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form, e.g., a powder or granules, optionally mixed with accessory ingredients, e.g., binders, lubricants, inert diluents, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

**[322]** A syrup or suspension may be made by adding the active compound to a concentrated, aqueous solution of a sugar, e.g., sucrose, to which may also be added any accessory ingredients. Such accessory ingredients)

may include flavoring, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, e.g., as a polyhydric alcohol, for example, glycerol or sorbitol.

**[323]** Formulations for rectal administration may be presented as a suppository with a conventional carrier, e.g., cocoa butter or Witepsol S55 (trademark of Dynamite Nobel Chemical, Germany), for a suppository base.

**[324]** Formulations suitable for parenteral administration conveniently comprise sterile aqueous preparation of the active compound that is preferably isotonic with the blood of the recipient. Thus, such formulations may conveniently contain distilled water, 5% dextrose in distilled water or saline. Useful formulations also comprise concentrated solutions or solids containing the compound of formula (IA) or (IB) that upon dilution with an appropriate solvent give a solution suitable for parental administration above.

**[325]** Topical formulations include ointments, creams, gels and lotions that may be prepared by conventional methods known in the art of pharmacy. In addition to the ointment, cream gel, or lotion base and the active ingredient, such topical formulation may also contain preservatives, perfumes, and additional active pharmaceutical agents.

**[326]** Solutions for use as eyedrops are preferentially prepared by first aseptically mixing of all the necessary ingredients i.e. the active substance, salts and lubricant. If necessary the pH is adjusted to 5-7 using solutions of NaOH, KOH, HCl or boric acid. The solution is then sterilized by autoclaving or sterile filtration and filled on one dose packages.

**[327]** Solutions can also be prepared by first preparing solutions of each of the ingredients and then sterilizing these solutions in the same manner as above before finally mixing and filling the solutions on one dose packages under aseptic conditions.

[328] In addition to the aforementioned ingredients, the formulations of this invention may further include one or more optional accessory ingredient(s) utilized in the art of pharmaceutical formulations, e.g., diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, suspending agents, preservatives (including antioxidants) and the like.

### EXAMPLES - Pharmaceutical Formulations

#### (A) Transdermal System - for 1000 patches

Ingredients	Amount
Active compound	100g
Silicone fluid	450g
Colloidal silicon dioxide	2g

[329] The silicone fluid and active compound are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequent heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin, and an impermeable backing membrane made of a polyester multi-laminate material. The resulting laminated sheet is then cut into 10 sq. cm patches.

#### (B) Oral Tablet - For 1000 Tablets

Ingredients	Amount
Active compound	50g

Ingredients	Amount
Starch	50g
Magnesium Stearate	5g

**[330]** The active compound and the starch are granulated with water and dried. Magnesium stearate is added to the dried granules and the mixture is thoroughly blended. The blended mixture is compressed into tablets.

(C) Injection - for 1000, 1mL Ampules

Ingredients	Amount
Active compound	10g
Buffering Agents	q.s.
Propylene glycol	400mg
Water for injection	q.s.1000m L

**[331]** The active compound and buffering agents are dissolved in the propylene glycol at about 50°C. The water for injection is then added with stirring and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving.

(D) Continuous Injection - for 1000 mL

Ingredients	Amount
Active compound	10g
Buffering agents	q.s.
Water for injection	q.s.1000m L

Ingredients	Amount

## (E) Eye Drops - for 100 mL

Ingredients	Amount
Active compound	0.01-1.0 g
Sodium chloride	0.5-0.09 g
Carbachol chloride	0.01-1.0 g
Boric acid	1.15-3.0 g
Water for injection	q.s. 100mL

[332] The eyedrops according to the formulations suggested can be applied directly to the eye either upon need or 3-4 times daily.

[333] An aerosol propellant suitable for use in an inhaler can be prepared similar to that described in US Patent 6,509,005 to Peart *et al.*, which is incorporated by reference.

## (B) Aerosol propellant

Ingredients	Amount
Active compound	0.13%
Ethanol	~5%
Hydrofluoroalkane propellant	95%

[334] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents, modifications and

variations to the specific embodiments of the invention described herein. For example, other excipients may be utilized in preparing the pharmaceutical formulations. In addition, some of the compounds described herein contain one or more asymmetric centers and may therefore give rise to enantiomers and diastereomers as well as their racemic and resolved, enantiomerically pure or diastereomerically pure forms, and pharmaceutically acceptable salts thereof. Moreover, it will be appreciated that the general representation of such paired variables as  $R^3$  and  $R^4$ , in formula IA, is not to be construed as to represent a particular orientation of the paired members. Accordingly, it is not intended that the present invention be limited to the specifics of the foregoing description of the preferred embodiments and example compounds, but rather as being limited only by the scope of the invention as defined in the claims appended hereto, including enantiomeric, diastereomeric and pharmaceutical salt forms.

## References

- [335] Baraldi PG, Cacciari B, Spalluto G, Pineda de las Infantas y Villatoro MJ, Zocchi C, Dionisotti S, Ongini E. (1996).  
Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine derivatives: potent and selective A2A adenosine antagonists. *J Med Chem.* 39: 1164-1171.
- [336] Baraldi PG, Cacciari B, Spalluto G, Bergonzoni M, Dionisotti S, Ongini E, Varani K, Borea PA. (1998). Design, synthesis and biological evaluation of a second generation of  
pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines as potent and selective A2A adenosine receptor antagonists. *J Med Chem* 41: 2126-2133.
- [337] Baraldi PG, Cacciari B, Romagnoli R, Spalluto G, Klotz K-N, Leung E, Varani K, Gessi S, Merighi S, Borea PA. (1999). Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine derivatives as highly potent and selective human A3 adenosine receptor antagonists. *J Med Chem* 42: 4473-4478.
- [338] Baraldi PG, Cacciari B, Romagnoli R, Merighi S, Varani K, Borea PA,

- Spalluto G. (2000). A3 Adenosine receptor ligands; history and perspectives. *Med Res Rev* 20: 103-128.
- [339] Baraldi PG, Cacciari B, Romagnoli R, Klotz, K-N, Spalluto G., Varani K, Gessi S., Merighi S, Borea PA (2001).  
Pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives as adenosine receptor ligands: a search for A213 adenosine receptor. *Drug Dev Res.*, 53, 225-235.
- [340] Boyle DL, Sajjadi FG, Firestein GS. (1996). Inhibition of synoviocyte collagenase gene expression by adenosine receptor stimulation. *Arthritis Rheum* 39: 923-930.
- [341] Bradford MM. ( 1976). A rapid and sensitive method for the quantification of microgram quantities of protein utilizing the principle of protein dye-binding. *Anal Biochem* 72: 248-254.
- [342] Cheng Y.C., Prusoff W.H. (1973). Relationships between the inhibition constant ( $K_i$ ) and the concentration of inhibitor which causes 50 per cent inhibition ( $IC_{50}$ ) of an enzymatic reaction. *Biochem. Pharmacol.*, 22: 3099-3 108.
- [343] Daly JW, Butts-Lamb P, Padgett W. (1983). Subclasses of adenosine receptors in the central nervous system: interaction with caffeine and related methylxanthines. *Cell Mol Neurobiol* 3: 69-80.
- [344] De Zwart M, Vcllinga RC, Beukers.MW, Sleegers DF, von Frijtag Drabbe Kunzel JK, de Groote M, Ijzerman AP. (1999). Potent antagonist for the human adenosine.A2B receptor. Derivatives of the triazolotriazine adenosine receptor antagonist ZM241385 with high affinity, *Drug Dev Res* 48: 95-103.
- [345] Dubey RK, Gillasple DG, Osaka K, Suzuki F, Jackson EK. (1996). Adenosine inhibits growth of rat aortic smooth muscle cells: possible role of A2B receptors. *Hypertension* 27: 786-793.



- [346] Feoktistov I, Biaggioni I. 1995. Adenosine A2B receptors evoke interleukine-S secretion in human mast cells: an enprofylline-sensitive mechanism with implication for asthma. *J. Clin Invest* 96: 1979-1986.
- [347] Feoktistov I, Bilaggioni I. (1997). Adenosine A2B receptors. *Pharmacol Rev* 49: 381-402.
- [348] Feoktistov I, Bilaggioni I. (1998). Pharmacological characterization of adenosine A2B receptors. *Biochem Pharmacol* 55: 627-633.
- [349] Feoktistov I, Wells J, Biaggioni I. (1998), Adenosine A2B receptors as therapeutic targets. *Drug Dev. Res* 45: 198-206.
- [350] Haynes JJ, Obikao B, Thompson V,"J, Downey J. (1995). Adenosine-induced vasodilation receptor characterization in pulmonary circulation. *Am J Physiol* 26S: H1862-H1868.
- [351] Jacobson KA, Ijzerman AP, Linden J. (1999). 1,3-Dialkylxanthine derivatives having high potency as antagonists at human A2B adenosine receptors. *Drug Dev. Res* 47: 45-53.
- [352] Ji X-D, Jacobson KA. (1999). Use of triazolotriazine [3H]-ZM241385 as a radioligand at recombinant human A2B adenosine receptors. *Drug Des Discov* 16: 217-226.
- [353] Ji X-D, Kim Y-C, Ahem D.G., Linden J., Jacobson KA. (2001). [3H]-MRS-1754, a selective antagonist radioligand for A2B adenosine receptors. *Biochem Pharmacol.*, 61: 657-663.
- [354] Kim Y-C, de Zwart M., Chang L, Moro S, von Frijtag Drabbe Kunzel JK, de Groote M, Melman N, Ijzerman AP, Jacobson KA. (1998). Derivatives of the triazoloquinazoline adenosine antagonist (CGS 15943) having high potency at the human A2B and A3 receptor subtypes. *J Med Chem* 41: 2835-2845.
- [355] Kim Y-C, Karton Y, Ji X-D, Melman N, Linden J, Jacobson KA. (1999). Acyl-hydrazide derivatives of a xanthine carboxylic congener (XCC) as

selective antagonists at human A<sub>2B</sub> adenosine receptors. *Drug Dev Res* 47: 178-188.

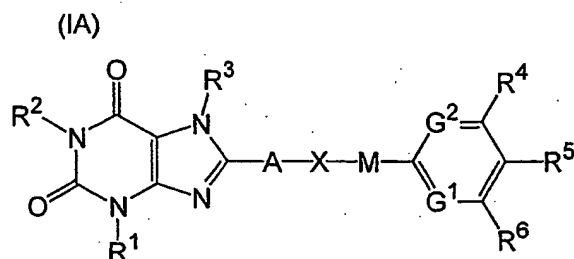
- [356] Kim Y-C, Ji X-D, Melman N, Linden J, Jacobson KA. (2000). Aniide derivatives of an 8-phenylxanthine carboxylic congener are highly potent and selective antagonists at human A<sub>2B</sub> adenosine receptors. *J Med Chem* 43: 1165-1172.
- [357] Klotz KN, Hessling J, Hegler J, Owman C, Kull B, Fredholm BB, Lohse MJ. (1998). Comparative pharmacology of human adenosine receptor subtypes characterization of stably transfected receptors in CHO cells. *Naunyn-Schmied. Arch Pharm.* 357: 1-9.
- [358] Londos C, Cooper DMF, Wolff J. (1980). Subclasses of external adenosine receptors. *Proc Natl Acad Sci USA* 77: 2551-2554.
- [359] Marquardt DL, Walker LL, Heinemann S. (1994). Cloning of two adenosine receptor subtypes from mouse bone marrow derived mast cells. *J Immunol* 152: 4508-4515.
- [360] Mateo J, Castro E, Zwiller J, Aunis D, Miras-Portugal MT. (1995). 5-(N-ethylcarboxamido)-adenosine inhibits Ca<sup>2+</sup> influx and activates a protein phosphatase in bovine adrenal chromaffin cells. *J Neurochem* 64: 77-84.
- [361] Murthy KS, McHenry L, Grider JR, Makhoul GM. (1995). Adenosine A<sub>1</sub> and A<sub>2B</sub> receptors coupled to distinct interactive signaling pathways in intestinal muscle cells. *J Pharmacol Exp Ther* 274: 243-2-46.
- [362] Munson PJ, Rodbard D. (1980). Ligand: a versatile computerized approach for the characterization of ligand binding systems. *Anal. Biochem.*, 107: 220-239.
- [363] Varani K, Gessi S, Dionisotti S, Ongini E, Borea PA. (1998). [3H]-SCH58261 labelling of functional A<sub>2A</sub> adenosine receptors in human neutrophil membranes. *Br. J. Pharmacol.*, 123: 1723-1731.
- [364] Varani K, Merighi S, Gessi S, Klotz K-N, Leung E, Baraldi PG, Cacciari

B, Romagnoli R, Spallato P, Borea PA. (2000). [3H]-MRE3008F20: a novel antagonist radioligand for the pharmacological and biochemical characterization of human A3 adenosine receptors. *Mol. Pharmacol.*, 57: 968-975.

[365] Zocchi C, Ongini E, Ferrara S, Baraldi PG, Dionisotti S. (1996). Binding of the radioligand [3H]-SCH58261, a new non-xanthine A2A adenosine receptor antagonist, to rat striatal membranes. *Br J Pharmacol.* 117: 1381-1386.

What is claimed is:

[c1] Adenosine A<sub>2B</sub> receptor antagonist compound of general formula I :



wherein:

R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl;

R<sup>3</sup> is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl);

A is a carbon-carbon bond, alkyl chain of one to four carbons, alkenyl chain of two to four carbons, or alkynyl chain of two to four carbons;

X is a five or six-membered heteroaromatic ring, containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen;

M is a (C<sub>1</sub> to C<sub>8</sub>)alkylene, (C<sub>2</sub> to C<sub>8</sub>)alkenylene, or (C<sub>2</sub> to C<sub>8</sub>)alkynylene, wherein at least one of the carbon atoms of the alkylene, alkenylene, or alkynylene group is present as a carbonyl, and one or more of the remaining carbon atoms of the alkylene, alkenylene, or alkynylene group may be replaced by -O-, -N(R<sup>7</sup>)-, -S-, -S(O)-, or SO<sub>2</sub>-;

G<sup>1</sup> and G<sup>2</sup> are independently CH or N;

$R^4$ ,  $R^5$  and  $R^6$  are independently hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>)alkenyl, (C<sub>2</sub> to C<sub>5</sub>)alkynyl, (C<sub>6</sub> to C<sub>10</sub>)aryl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl, acyl, alkoxy, aralkoxyalkylthio, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, iodo, nitro, cyano, azido, hydroxy, sulfhydryl, S(O)alkyl, S(O)<sub>2</sub>alkyl, CO<sub>2</sub>H, SO<sub>3</sub>H, or five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from nitrogen, oxygen, or sulfur; or

taken together either  $R^4$  and  $R^5$  or  $R^5$  and  $R^6$  form a carbocyclic or heterocyclic fused ring selected from the group of fused rings comprising -OCH<sub>2</sub>O-, -OCH(R<sup>7</sup>)O-, -OC(R<sup>7</sup>)<sub>2</sub>O-, -OCH<sub>2</sub>CH<sub>2</sub>O-, OCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>O-, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O-, -OCH=CH-, -CH=CH-O-, -O-CH=CH-O-, -CH=CH-CH=CH-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; and

$R^7$  is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl).

- [c2] A method of treating diseases mediated by adenosine A<sub>2B</sub> receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c1].
- [c3] The method of claim [c2], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.

- [c4] The method of claim [c2], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of asthma.
- [c5] The method of claim [c2], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.
- [c6] A compound selected from the group of compounds consisting of:
- 8-(3-amino-1-methyl-1*H*-pyrazol-5-yl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione;
  - [3-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)isoxazol-5-yl]methyl-benzoate;
  - 8-(1-methyl-4-nitro-1*H*-pyrrol-2-yl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione;
  - 4-[[5-(1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]amino]-4-oxobutanoic acid;
  - tert*-butyl 4-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]amino]-4-oxobutylcarbamate;
  - 4-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]amino]-4-oxobutan-1-aminium;
  - N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-phenylacetamide;
  - 2-(2,4-dichlorophenoxy)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;
  - 2-(3-methoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;
  - N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-isobutylphenyl)acetamide;
  - N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-nitrophenyl)acetamide;
  - 2-[4-benzyloxyphenyl]-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;
  - 2-[4-hydroxyphenyl]-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;
  - (2*S*)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-phenylpropanamide;
  - (2*R*)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-phenylpropanamide;
  - {3-[(*E*)-2-(1,3-dipropyl-7-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)vinyl]isoxazol-5-yl}methyl benzoate;

2-(4-chlorophenoxy)-*N*-[5-(1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-fluorophenyl)acetamide;

2-(4-methoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(3-chlorophenyl)acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(3-fluorophenyl)acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-[(*N,N*-dimethylamino)phenyl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-chlorophenyl)acetamide;

2-(3,4-dimethoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-[(2-(trifluoromethyl)benzyl)oxy]phenyl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-[(3-(trifluoromethyl)benzyl)oxy]phenyl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-(4-nitro-benzyloxy)phenyl)acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-[(3-(trifluoromethyl)phenyl)acetamide];

phenyl 4-[(*E*)-2-(7-methyl-1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)vinyl]-1-methyl-1*H*-pyrrole-2-carboxylate;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-5-yl]-2-phenylacetamide;

8-(1-methyl-3-nitro-1*H*-pyrazol-5-yl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione;

8-(5-amino-1-methyl-1*H*-pyrazol-3-yl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione;

8-(3-amino-1-methyl-1*H*-pyrazol-5-yl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione;

*N*-[5-(2,6-dioxo-1,3-dimethyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-phenylacetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(3,4-difluorophenyl)acetamide;

2-(2,3,4-trimethoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[4-(dimethylamino)phenyl]-*N'*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]urea;

*N*-(3-chlorophenyl)-*N'*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]urea;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-*N'*-(3-methoxyphenyl)urea;

2-[4-(benzyloxy)-3-methoxyphenyl]-N-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]acetamide;

2-(1,3-benzodioxol-5-yl)-N-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]acetamide;

N-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]-2-(4-hydroxy-3-methoxyphenyl)acetamide;

N-(4-methylphenyl)-2-[[5-(1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]oxy]acetamide;

N-(4-bromophenyl)-2-[[3-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-5-yl]oxy]acetamide;

N-(4-fluorophenyl)-2-[[3-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-5-yl]oxy]acetamide;

2-[[3-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-5-yl]oxy]-N-(4-fluorophenyl)acetamide;

2-[[3-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-5-yl]oxy]-N-(4-bromophenyl)acetamide;

2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]oxy]-N-(4-fluorophenyl)acetamide;

2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]oxy]-N-(4-bromophenyl)acetamide;

2-[[5-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]oxy]-N-(4-fluorophenyl)acetamide;

2-[[5-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]oxy]-N-(4-bromophenyl)acetamide;

N-1,3-benzodioxol-5-yl-2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]oxy]acetamide; and

2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]oxy]-N-(4-methoxyphenyl)acetamide.

1,3-di-n-propyl-8-(1-methyl-5-carboxy-1-H-pyrazol-3-yl)-xanthine

1-[5-(2,6-Dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yl]-3-(4-methoxy-phenyl)-urea

1,3-di-n-propyl-8-{5-[(4-sec-butyl-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[(4-methyl-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[(4-(morpholine-4-yl)-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[(4-carboxy-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[(3,4-dimethyl-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[(3,4-dimethyl-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[(3,4-dimethoxy-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine



1,3-di-n-propyl-8-{5-[(pyridin-4-yl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[2-oxo-2-(4-phenyl-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

8-(5-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-2-methyl-2H-pyrazol-3-yl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione

1,3-di-n-propyl-8-{5-[2-Oxo-2-(4-methyl-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

8-(5-{2-[4-(4-Benzyl-phenyl)-piperazin-1-yl]-2-oxo-ethoxy}-2-methyl-2H-pyrazol-3-yl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione

1,3-di-allyl-8-{5-[2-oxo-2-(4-phenyl-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{3-[(3,4-methylenedioxy-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine

1,3-di-n-propyl-8-{3-[(3,4-dimethoxy-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine

1,3-di-n-propyl-8-{3-[(4-fluoro-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine

1,3-di-n-propyl-8-{3-[(4-methoxy-phenylcarbamoyl)-methoxy]-isoxazol-5-yl}-xanthine

1,3-di-n-propyl-8-{6-[(4-iodo-phenylcarbamoyl)-methoxy]-pyridin-3-yl}-xanthine

1,3-di-n-propyl-8-{6-[(4-iodo-phenylcarbamoyl)-methoxy]-pyridazin-3-yl}-xanthine

*N*-1,3-benzodioxol-5-yl-2-[[5-(2,6-dioxo-1,3-diallyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]acetamide

1,3-di-n-propyl-8-{5-[(4-(ethoxycarbonyl)-phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-(2-hydroxypyridin-5-yl)-xanthine

1,3-diallyl-8-{5-[2-oxo-2-(4-(pyridin-2-yl)-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-diallyl-8-{5-[2-oxo-2-(4-(pyrimidin-2-yl)-piperazin-1-yl)-ethoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

1,3-di-n-propyl-8-{5-[(4-(aminosulfonyl)phenylcarbamoyl)-methoxy]-2-methyl-2H-pyrazole-3-yl}-xanthine

[c7] A method of treating diseases mediated by adenosine A<sub>2B</sub> receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c6].

[c8] The method of claim [c7], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases

involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.

[c9] The method of claim [c7], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of asthma.

[c10] The method of claim [c7], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

[c11] A highly potent adenosine A<sub>2B</sub> receptor antagonist compound selected from the group consisting of:

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-phenylacetamide;

2-(3-methoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-nitrophenyl)acetamide;

2-[4-benzyloxyphenyl]-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

2-[4-hydroxyphenyl]-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-fluorophenyl)acetamide;

2-(4-methoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(3-chlorophenyl)acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(3-fluorophenyl)acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-[4-(*N,N*-dimethylamino)phenyl]acetamide;  
*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-chlorophenyl)acetamide;  
2-(3,4-dimethoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;  
*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-[[2-(trifluoromethyl)benzyl]oxy]phenyl)acetamide;  
*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-[[3-(trifluoromethyl)benzyl]oxy]phenyl)acetamide;  
*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-{4-nitro-benzyl}oxy)phenyl)acetamide;  
*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-5-yl]-2-phenylacetamide;  
8-(5-amino-1-methyl-1*H*-pyrazol-3-yl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione;  
*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(3,4-difluorophenyl)acetamide;  
*N*-[4-(dimethylamino)phenyl]-*N'*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]urea;  
*N*-(3-chlorophenyl)-*N'*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]urea;  
*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-*N'*-(3-methoxyphenyl)urea;  
2-[4-(benzyloxy)-3-methoxyphenyl]-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;  
2-(1,3-benzodioxol-5-yl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;  
*N*-(4-bromophenyl)-2-[[3-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-5-yl]oxy]acetamide;  
2-[[3-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-5-yl]oxy]-*N*-(4-bromophenyl)acetamide;  
2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]-*N*-(4-fluorophenyl)acetamide;  
2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]-*N*-(4-bromophenyl)acetamide;  
2-[[5-(1,3-diisobutyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]-*N*-(4-bromophenyl)acetamide;  
*N*-1,3-benzodioxol-5-yl-2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]acetamide; and  
2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]-*N*-(4-methoxyphenyl)acetamide.

[c12] A very potent and highly selective adenosine A<sub>2B</sub> receptor antagonist selected from the group consisting of:

2-(3-methoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-(4-nitrophenyl)acetamide;

2-[4-benzyloxyphenyl]-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

2-[4-hydroxyphenyl]-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-[4-(*N,N*-dimethylamino)phenyl]acetamide;

2-(3,4-dimethoxyphenyl)-*N*-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]acetamide;

8-(3-amino-1-methyl-1*H*-pyrazol-5-yl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione;

*N*-[5-(2,6-dioxo-1,3-dimethyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]-2-phenylacetamide;

*N*-(4-methylphenyl)-2-[[5-(1,3-dipropyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]acetamide; and

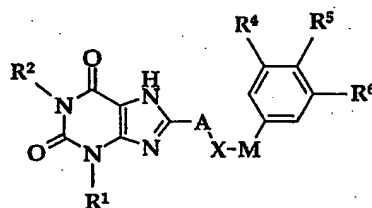
2-[[5-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-1-methyl-1*H*-pyrazol-3-yl]oxy]-*N*-(4-methoxyphenyl)acetamide.

- [c13] A method of treating diseases mediated by adenosine A<sub>2B</sub> receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c11] or claim [c12].
- [c14] The method of claim [c13], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.

[c15] The method of claim [c13], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of asthma.

[c16] The method of claim [c13], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

[c17] Adenosine A<sub>2b</sub> receptor antagonist compound of the formula :

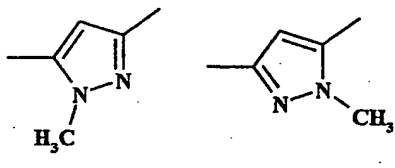


wherein:

R<sup>1</sup> and R<sup>2</sup> are independently (C<sub>1</sub> to C<sub>3</sub>)alkyl or allyl;

A is a carbon-carbon bond;

X is selected from the group consisting of

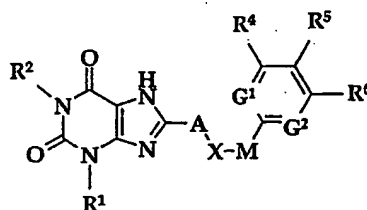


M is selected from the group consisting of -NHC(O)CH<sub>2</sub>-, -NHC(O)CH<sub>2</sub>O-, -NHC(O)CH(CH<sub>3</sub>)-, or NHC(O)NH-;

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>)alkenyl, (C<sub>2</sub> to C<sub>5</sub>)alkynyl, (C<sub>8</sub> to C<sub>10</sub>)aryl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl, acyl, alkoxy, aralkoxy, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, nitro, hydroxy, CO<sub>2</sub>H, or five or six membered heterocyclic or heteroaromatic

ring containing one to four heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen; or taken together either R<sup>4</sup> and R<sup>5</sup> or R<sup>5</sup> and R<sup>6</sup> form a carbocyclic or heterocyclic fused ring selected from the group of fused rings comprising -OCH<sub>2</sub>O-.

- [c18] A method of treating diseases mediated by adenosine A<sub>2B</sub> receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c17].
- [c19] The method of claim [c18], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.
- [c20] The method of claim [c18], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of asthma.
- [c21] The method of claim [c18], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.
- [c22] Adenosine A<sub>2b</sub> receptor antagonist compound of the formula:

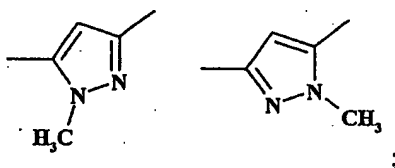


wherein:

$R^1$  and  $R^2$  are independently (C<sub>1</sub> to C<sub>4</sub>)alkyl;

A is a carbon-carbon bond;

X is selected from the group consisting of



M is OCH<sub>2</sub>C(O)NH;

G<sup>1</sup> and G<sup>2</sup> are independently CH or N;

$R^4$ ,  $R^5$  and  $R^6$  are independently hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>)alkenyl, (C<sub>2</sub> to C<sub>5</sub>)alkynyl, (C<sub>6</sub> to C<sub>10</sub>)aryl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl, acyl, alkoxy, aralkoxy, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, nitro, hydroxy, CO<sub>2</sub>H, or a five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from the group consisting of oxygen, or sulfur, and nitrogen, or taken together either  $R^4$  and  $R^5$  or  $R^5$  and  $R^6$  form a carbocyclic or heterocyclic fused ring selected from the group comprising -OCH<sub>2</sub>O-.

[c23] A method of treating diseases mediated by adenosine A<sub>2B</sub> receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c22].

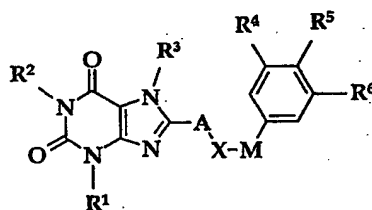
[c24] The method of claim [c23], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic

obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.

[c25] The method of claim [c23], wherein the treatment of diseases mediated by adenosine  $A_{2B}$  receptors involves treating of asthma.

[c26] The method of claim [c23], wherein the treatment of diseases mediated by adenosine  $A_{2B}$  receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

[c27] Adenosine  $A_{2b}$  receptor antagonist compound of the formula :



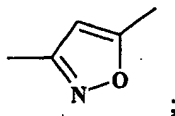
wherein:

$R^1$  and  $R^2$  are independently ( $C_1$  to  $C_3$ )alkyl ;

$R^3$  is hydrogen or methyl;

A is selected from the group consisting of a carbon-carbon bond or  $-CH=CH-$ ;

X is selected from the group consisting of



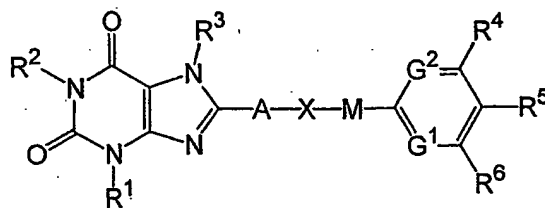


M is CH<sub>2</sub>OC(O);

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>)alkenyl, (C<sub>2</sub> to C<sub>5</sub>)alkynyl, (C<sub>6</sub> to C<sub>10</sub>)aryl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl, acyl, alkoxy, aralkoxy, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, nitro, hydroxy, CO<sub>2</sub>H, or five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen.

- [c28] A method of treating diseases mediated by adenosine A<sub>2B</sub> receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c27].
- [c29] The method of claim [c28], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.
- [c30] The method of claim [c28], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of asthma.
- [c31] The method of claim [c28], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

[c32] Adenosine A<sub>2b</sub> receptor antagonist of the formula:



wherein:

R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl;

R<sup>3</sup> is hydrogen, (C<sub>1</sub> to C<sub>4</sub>)alkyl, (C<sub>2</sub> to C<sub>5</sub>) alkenyl, or (C<sub>2</sub> to C<sub>5</sub> alkynyl);

A is a carbon-carbon bond, alkyl chain of one to four carbons, alkenyl chain of two to four carbons, or alkynyl chain of two to four carbons;

X is independently a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen; a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen, substituted at any position with a substituent selected from lower alkyl, amino, hydroxy, alkyloxy, acyloxy, acylamino; or a five or six-membered heteroaromatic ring containing one to four heteroatoms, selected from nitrogen, oxygen, or sulfur, provided that at least one heteroatom is nitrogen, substituted at any two positions with substituents selected independently from lower alkyl, amino, hydroxy, alkyloxy, acyloxy, acylamino.

M is a (C<sub>1</sub> to C<sub>8</sub>)alkylene, (C<sub>2</sub> to C<sub>8</sub>)alkenylene, or (C<sub>2</sub> to C<sub>8</sub>)alkynylene, wherein at least one of the carbon atoms of the alkylene, alkenylene, or

alkynylene group is present as a carbonyl, and one or more of the remaining carbon atoms of the alkylene, alkenylene, or alkynylene group may be replaced by  $-O-$ ,  $-N(R^7)-$ ,  $-S-$ ,  $-S(O)-$ ,  $-SO_2-$ ; or a carbon substituted with a lower alkyl group.

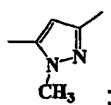
$G^1$  and  $G^2$  are independently CH or N;

$R^4$ ,  $R^5$  and  $R^6$  are independently hydrogen,  $(C_1$  to  $C_4)$ alkyl,  $(C_2$  to  $C_5)$ alkenyl,  $(C_2$  to  $C_5)$ alkynyl,  $(C_6$  to  $C_{10})$ aryl,  $(C_7$  to  $C_{14})$ aralkyl,  $(C_8$  to  $C_{14})$ aralkenyl, or  $(C_8$  to  $C_{14})$ aralkynyl, acyl, alkoxy, aralkoxyalkylthio, amino, substituted amino, disubstituted amino, fluoro, chloro, bromo, iodo, nitro, cyano, azido, hydroxy, sulfhydryl,  $S(O)$ alkyl,  $S(O)_2$ alkyl,  $CO_2H$ ,  $SO_3H$ , or five or six membered heterocyclic or heteroaromatic ring containing one to four heteroatoms selected from nitrogen, oxygen, or sulfur; or

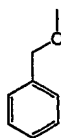
taken together either  $R^4$  and  $R^5$  or  $R^5$  and  $R^6$  independently may form a carbocyclic or heterocyclic fused ring selected from the group of fused rings comprising  $-OCH_2O-$ ,  $-OCH(R^7)O-$ ,  $-OC(R^7)_2O-$ ,  $-OCH_2CH_2O-$ ,  $OCH_2CH_2-$ ,  $-CH_2CH_2O-$ ,  $-OCH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2O-$ ,  $-OCH=CH-$ ,  $-CH=CH-O-$ ,  $-O-CH=CH-O-$ ,  $-CH=CH-CH=CH-$ ,  $-CH_2CH_2CH_2-$  and  $-CH_2CH_2CH_2CH_2-$ ; and

$R^7$  is hydrogen,  $(C_1$  to  $C_4)$ alkyl,  $(C_2$  to  $C_5)$  alkenyl, or  $(C_2$  to  $C_5)$  alkynyl.

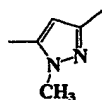
[c33] The compound (AS16) of claim [c32] wherein  $R^1$  and  $R^2$  are each n-propyl, A is a carbon-carbon bond; X is



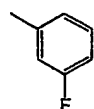
M is  $-NH-C(O)-CH_2-$ ;  $G^1$  and  $G^2$  are each CH;  $R^4$  and  $R^6$  are H; and  $R^5$  is



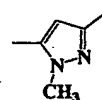
[c34] The compound (AS25) of claim [c32] wherein  $R^1$  and  $R^2$  are each n-propyl;  $R^3$  is H; A is a carbon-carbon bond; X is



M is  $-NH-C(O)-CH_2-$ ;  $G^1$  and  $G^2$  are each CH;  $R^4$  and  $R^5$  are each H; and  $R^6$  is

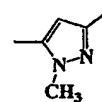


[c35] The compound (AS28) of claim [c32] wherein  $R^1$  and  $R^2$  are each n-propyl;  $R^3$  is H; A is a carbon-carbon bond; X is



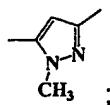
M is  $-NH-C(O)-CH_2-$ ;  $G^1$  and  $G^2$  are each CH;  $R^4$  is H; and  $R^5$  and  $R^6$  are each methoxy.

[c36] The compound (AS53) of claim [c32] wherein  $R^1$  and  $R^2$  are each n-propyl;  $R^3$  is H; A is a carbon-carbon bond; X is



; M is  $-NH-C(O)-NH-$ ;  $G^1$  and  $G^2$  are each CH;  $R^4$  and  $R^6$  are H; and  $R^5$  is  $-N(CH_3)_2$ .

[c37] The compound (AS68) of claim [c32] wherein  $R^1$  and  $R^2$  are each n-propyl;  $R^3$  is H; A is a carbon-carbon bond; X is

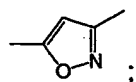


M is  $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ;  $\text{G}^1$  and  $\text{G}^2$  are each CH;  $\text{R}^4$  and  $\text{R}^5$  are together.

$-\text{O}-(\text{CH}_2)-\text{O}-$ ;

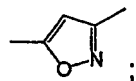
and  $\text{R}^6$  is H.

[c38] The compound (AS74) of claim [c32] wherein  $\text{R}^1$  and  $\text{R}^2$  are each  $\text{CH}_2=\text{CHCH}_2-$ ;  $\text{R}^3$  is H; M is a carbon-carbon bond; X is



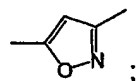
M is  $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ;  $\text{G}^1$  and  $\text{G}^2$  are each CH;  $\text{R}^4$  is H; and  $\text{R}^5$  and  $\text{R}^6$  are together  $-\text{O}-\text{CH}_2-\text{O}-$ .

[c39] The compound (AS75) of claim [c32] wherein  $\text{R}^1$  and  $\text{R}^2$  are each n-propyl; A is a carbon-carbon bond; X is



M is  $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ;  $\text{G}^1$  and  $\text{G}^2$  are each CH;  $\text{R}^4$  and  $\text{R}^6$  are each H; and  $\text{R}^5$  is methoxy.

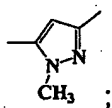
[c40] A compound (AS76) of claim [c32] wherein  $\text{R}^1$  and  $\text{R}^2$  are each n-propyl; A is a carbon-carbon bond; X is



M is  $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ;  $\text{G}^1$  and  $\text{G}^2$  are each CH;  $\text{R}^4$  is H; and  $\text{R}^5$  and  $\text{R}^6$  are each methoxy.

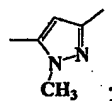
[c41] A compound (AS94) of claim [c32] wherein  $\text{R}^1$  and  $\text{R}^2$  are each n-

propyl; A is a carbon-carbon bond; X is



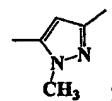
M is  $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ;  $\text{G}^1$  and  $\text{G}^2$  are each CH;  $\text{R}^4$  and  $\text{R}^6$  are H; and  $\text{R}^5$  is  $-\text{C}(\text{O})-\text{O}-\text{CH}_2-\text{CH}_3$ .

[c42] The compound (AS95) of claim [c32] wherein  $\text{R}^1$  and  $\text{R}^2$  are each n-propyl; A is a carbon-carbon bond; X is



M is  $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ;  $\text{G}^1$  and  $\text{G}^2$  are each CH;  $\text{R}^4$  and  $\text{R}^6$  are H; and  $\text{R}^5$  is  $-\text{CO}_2\text{H}$ .

[c43] The compound (AS101) of claim [c32] wherein  $\text{R}^1$  and  $\text{R}^2$  are each n-propyl;  $\text{R}^3$  is H; A is a carbon-carbon bond; X is



M is  $-\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$ ;  $\text{G}^1$  and  $\text{G}^2$  are each CH;  $\text{R}^4$  and  $\text{R}^5$  are each methoxy; and  $\text{R}^6$  is H.

[c44] A method of treating diseases mediated by adenosine  $\text{A}_{2\text{B}}$  receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c32].

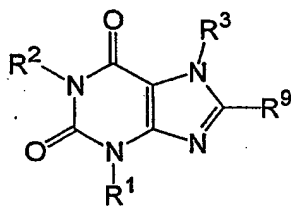
[c45] The method of claim [c44], wherein the treatment of diseases mediated by adenosine  $\text{A}_{2\text{B}}$  receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including

Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.

[c46] The method of claim [c44], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves the treating of asthma.

[c47] The method of claim [c44], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves the treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

[c48] Adenosine A<sub>2b</sub> receptor antagonist compound of the formula:

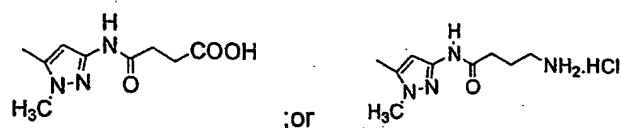


wherein:

R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, (C<sub>1</sub> to C<sub>8</sub>)alkyl, (C<sub>2</sub> to C<sub>8</sub>)alkenyl, (C<sub>2</sub> to C<sub>8</sub>)alkynyl, (C<sub>7</sub> to C<sub>14</sub>)aralkyl, (C<sub>8</sub> to C<sub>14</sub>)aralkenyl, or (C<sub>8</sub> to C<sub>14</sub>)aralkynyl;

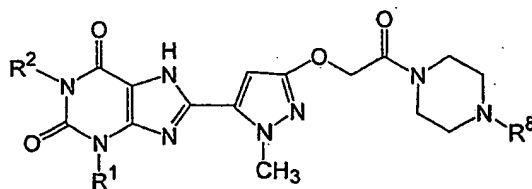
R<sup>3</sup> is H or (C<sub>1</sub> to C<sub>8</sub>)alkyl; and

R<sup>9</sup> is independently a phenyl or pyrazole ring; a phenyl or pyrazole ring substituted at any position with amino, lower alkyl, or carboxyl; a phenyl or pyrazole ring substituted at any two positions with a substituent selected from amino, lower alkyl, and carboxyl;



- [c49] A method of treating diseases mediated by adenosine A<sub>2B</sub> receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c48].
- [c50] The method of claim [c49], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.
- [c51] The method of claim [c49], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves the treating of asthma.
- [c52] The method of claim [c49], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.
- [c53] Adenosine A<sub>2B</sub> receptor antagonist compound of the formula:





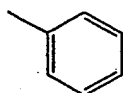
wherein:

$R^1$  and  $R^2$  are independently hydrogen, (C1 to C8)alkyl, (C2 to C8)alkenyl, (C2 to C8)alkynyl, (C7 to C14)aralkyl, (C8 to C14)aralkenyl, or (C8 to C14)aralkynyl; and

$R^8$  is phenyl, halogen substituted phenyl, (C1 to C8)alkyl, or benzyl.

[c54] A compound (AS96) of claim [c53] wherein  $R^1$  and  $R^2$  are each

$\text{CH}_2=\text{CH}-\text{CH}_2-$ ; and  $R^8$  is



[c55] A method of treating diseases mediated by adenosine  $A_{2B}$  receptors comprising administering to a patient in need of treatment thereof an effective amount of a compound of claim [c53].

[c56] The method of claim [c55], wherein the treatment of diseases mediated by adenosine  $A_{2B}$  receptors involves treating a disorder selected from the group consisting of chronic and acute inflammatory diseases involving degranulation of mast cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting; impaired sensitivity to insulin including Type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, and impaired glucose tolerance; diseases in which angiogenesis is a key component of pathogenesis including solid tumors and angiogenic retinopathies; apnea of preterm infants; myocardial reperfusion injury; inflammatory bowel disease; and autoimmune disease, such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus.

- [c57] The method of claim [c55], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of asthma.
- [c58] The method of claim [c55], wherein the treatment of diseases mediated by adenosine A<sub>2B</sub> receptors involves treating of a disorder selected from the group consisting of microvascular abnormalities of the retina, retinopathy, prematurity, macular degeneration, and diabetic retinopathy.

Competition curves of compound AS 29 to human cloned  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$  adenosine receptors.

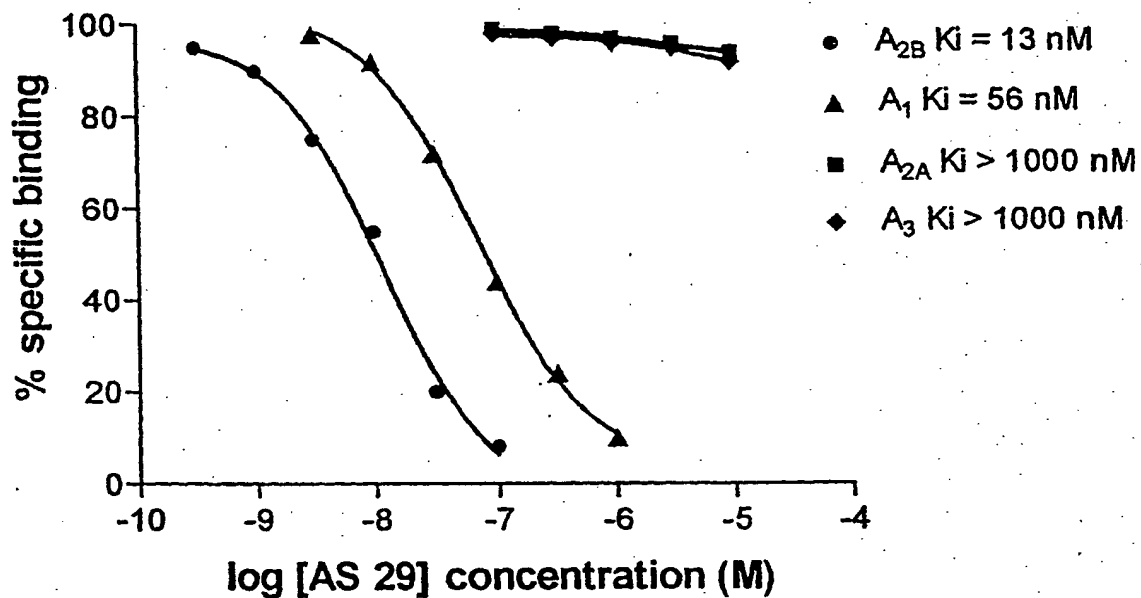


Figure 1

Competition curves of compound AS 57 to human cloned  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$  adenosine receptors.

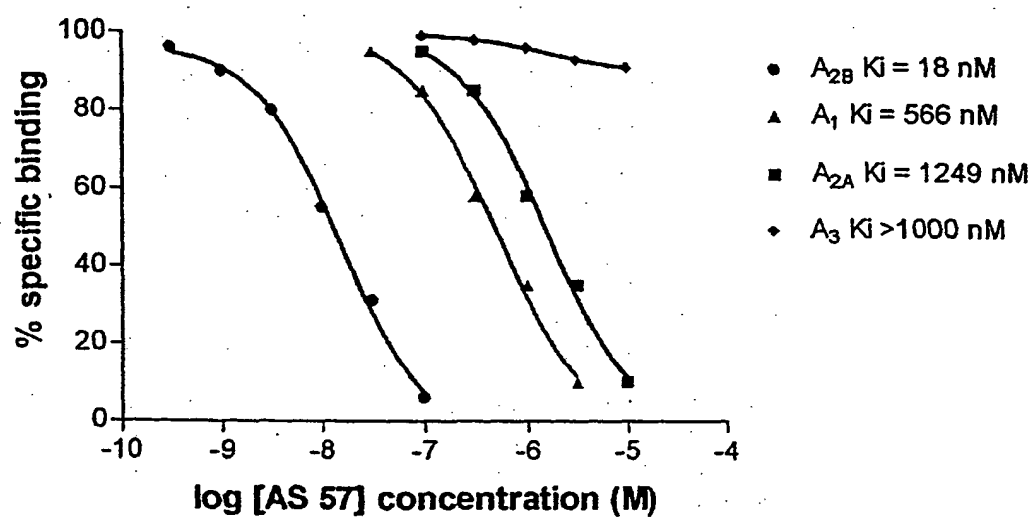


Figure 2

Competition curves of compound AS 64 to human cloned  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$  adenosine receptors.

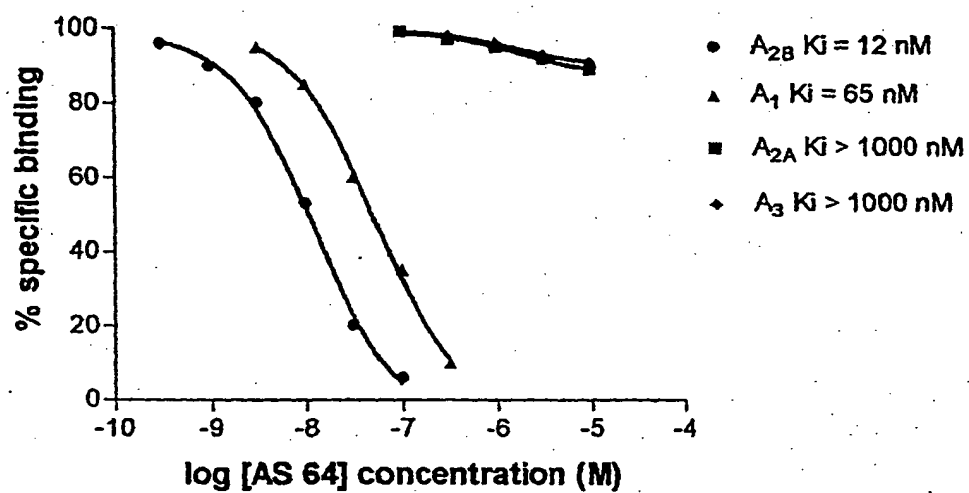


Figure 3

Competition curves of compound AS 68 to human cloned  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$  adenosine receptors.

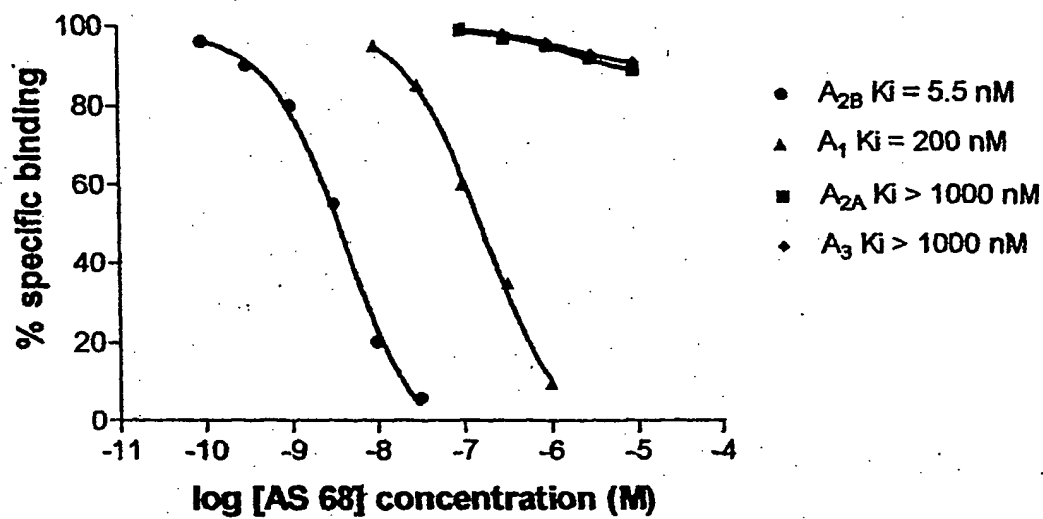
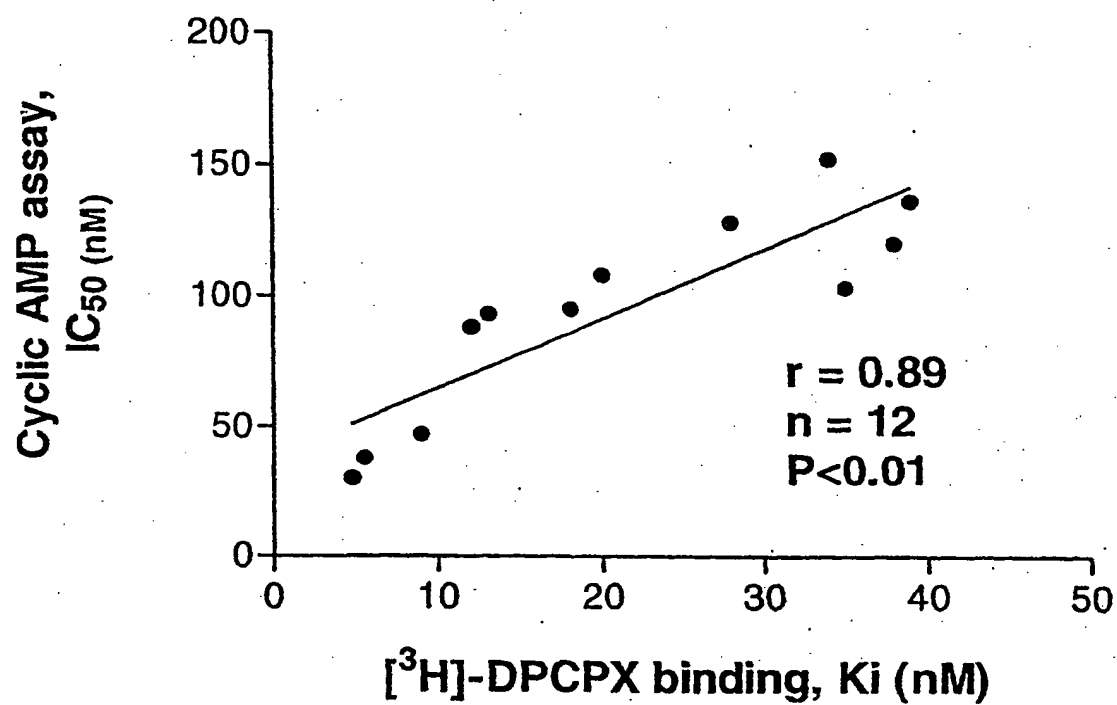


Figure 4

### Comparison between binding and functional data



**Figure 5**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau



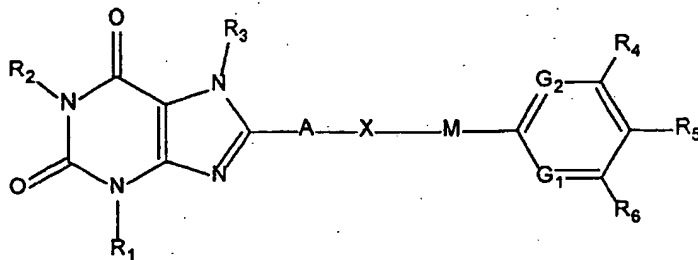
(43) International Publication Date  
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- (30) Priority Data:  
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- (71) Applicant: KING PHARMACEUTICALS RESEARCH AND DEVELOPMENT, INC. [US/US]; 7001 Weston Parkway, Suite 300, Cary, NC 27513 (US).
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- Published:  
— with international search report
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- (72) Inventors; and  
(75) Inventors/Applicants (*for US only*): BARALDI, Pier, Giovanni [—/IT]; Via Tulipani, 73, I-44100 Ferrara (IT). BOREA, Pier, A. [—/IT]; Via del Turco, 14, I-44100 Ferrara (IT).
- (74) Agents: KONIECZNY, J., Mark et al.; Edwards & Angell, LLP, P.O. Box 9169, Boston, MA 02209 (US).
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 8-HETEROARYL XANTHINE ADENOSINE A<sub>2B</sub> RECEPTOR ANTAGONISTS



(IA)

(57) Abstract: The present invention relates to compounds of formula (IA): the preparation thereof, pharmaceutical formulations thereof, and their use in medicine as potent or selective A<sub>2B</sub> adenosine receptor antagonists and their uses for treating asthma, autoimmune diseases and retinal vascular diseases.

WO 03/063800 A3



## INTERNATIONAL SEARCH REPORT

International application No.

PCT US03.03224

## A. CLASSIFICATION OF SUBJECT MATTER

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US CL : 514.263.34; 544 273

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/263.34; 544/273

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,117,878 A (LINDEN) 12 September 2000 (12.09.00), see the entire document.	1-58
A	US 5,935,964 A (BARALDI et al.) 10 August 1999 (10.08.99), see the entire document.	1-58

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

## \* Special categories of cited documents:

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08 May 2003 (08.05.2003)

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Facsimile No. (703)305-3230

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Authorized officer

Raymond J. Henley III

Telephone No. 703-308-1235